NOVEMBER 1953

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

THE MANAGEMENT OF DIABETES
Transcription of a Panel Meeting
GEORGE E. ANDERSON JOSEPH T. BEARDWOOD, Jr.
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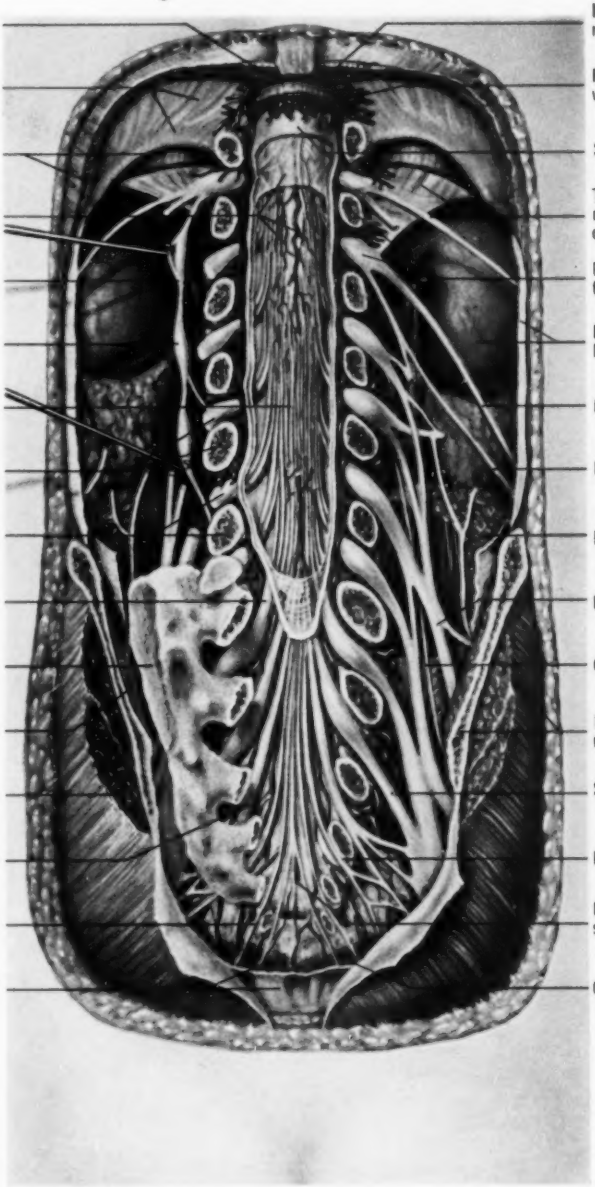

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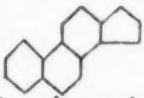
the symbol SCHERING denotes leadership in steroid hormone  research and manufacture -- including Cortogen in the most useful clinical forms. For systemic therapy, use Cortogen tablets or injection . For eye disorders use Cortogen ophthalmic suspension -- sterile . The Schering seal SCHERING appears on each tablet and package -- your assurance of quality.

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1. Moyer, J. H., et al.: Am. J. M. Sc. *225*:379 (April) 1953.
2. Mills, L. C., and Moyer, J. H.: A.M.A. Arch. Int. Med. *90*:587 (Nov.) 1952.
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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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THE LOW SODIUM SYNDROME: ITS ORIGINS AND VARIETIES*

LOUIS LEITER, RAYMOND E. WESTON and JACOB GROSSMAN

From the Medical Division, Montefiore Hospital, New York

THE classical low sodium syndrome[1-4] is closely related to the external depletion or internal segregation of sodium and its associated electrolytes. It is also inextricably associated with retention of water, overhydration of cells[5-8] and dilution of body electrolytes. This dilution phenomenon is particularly evident in congestive heart failure and other edematous states[3, 8-11] in which, indeed, it may under certain circumstances represent the primary basis for reduction in the concentration of extracellular sodium and for initiation of a clinical syndrome with some of the features seen in non-edematous, sodium-depleted individuals.† As a result, the differentiation between the effects of sodium depletion and sodium dilution in congestive heart failure becomes difficult in practice, if at all possible in theory. Yet, it is important to attempt to gauge the degree of sodium depletion since replacement of lost electrolyte may be the only effective therapeutic measure (Table I).

In addition to hyponatremia resulting from depletion and dilution, there is a third group of cases with chronic, "asymptomatic" hypona-

* Read in modified form at the Stated Meeting of The New York Academy of Medicine combined with the Section on Medicine, February 5, 1953.
Manuscript received April 1953.

† An impaired diuretic response to water is characteristic of both the depletion and dilution types of hyponatremia, whether of clinical or experimental origin[2,9,12-14].

TABLE I—CLINICAL VARIETIES OF HYPONATREMIA

Type and Cause	*Major Symptoms*	*Treatment*
1. Low Sodium Syndrome, by external loss or internal segregation of sodium.	Circulatory Collapse, Renal Insufficiency, Central Nervous Depression.	Correction of Sodium Deficit in Body Fluids.
2. Sodium Dilution Syndrome, by excessive retention of water (ADH, Pitressin).	Increasing Congestive Failure, Renal Insufficiency, "Water Intoxication."	For Basic Condition. Restrict Fluids. Withhold Salt.
3. Combined Low Sodium (Depletion) and Dilution Syndromes.	Mixture of above Groups.	Gradual Correction of Sodium Deficit. For Basic Condition.
4. Chronic Hyponatremia, due to nutritional hypo-osmolarity of cells.	Of Chronic Wasting Disease. None Referable to Low Serum Sodium.	For Basic Disease and Malnutrition.
5. Chronic Hyponatremia with Acute Low Sodium (Depletion) or Sodium Dilution Syndrome.	Mixture of above Groups.	Partial Correction of Sodium Deficit. For Basic Disease.

tremia associated with the prolonged malnutrition of advanced tuberculosis, cirrhosis of the liver, cardiac failure and other conditions.[15-18] In this group the primary disturbance seems to lie in the nutritional intracellular depletion and hypo-osmolarity. The reduced extracellular sodium concentration is a compensatory adjustment, and the regulatory mechanisms for sodium metabolism function, apparently, normally around the low level. Sodium depletion or dilution may develop in this group from the usual causes. Much confusion in diagnosis and treatment will arise if the previous chronic hyponatremia is unknown to the physician.

The low sodium syndrome came into prominence with advances in the treatment of cardiac edema, on the one hand, and with excessive non-saline hydration, postoperatively, of surgical patients, on the other hand. The administration of mercurial diuretics, at close intervals, to cardiac patients on strict low salt diets with a normal fluid intake, furnishes the

TABLE II—SYMPTOMS OF LOW SODIUM SYNDROME

1.	Central Nervous	— Apathy, Drowsiness, Confusion, Psychosis, Coma.
2.	Gastrointestinal	— Anorexia, No Thirst, Nausea, Vomiting, Cramps.
3.	Circulatory	— Tachycardia, Small Pulse, Postural Hypotension or Syncope, Collapse.
4.	Renal	— Oliguria, Anuria, Polyuria, Impaired Diuresis, Uremia, Acidosis or Alkalosis.
5.	Muscular	— Weakness, Cramps, Twitchings.
6.	Cutaneous	— Dehydration, Loss of Elasticity, Ischemia.
7.	Blood Chemical	— Low Serum Sodium and Variable Chloride, Bicarbonate and Potassium; Azotemia.

basis for the development of a low sodium syndrome.[3, 19, 20] Accelerating factors include extra sweating during hot weather, brief periods of anorexia and poor food intake, vomiting or diarrhea, repeated paracentesis or thoracentesis, or anything else associated with further net loss of sodium or dilution of body fluid.

In the surgical cases, the common combination of removal of gastrointestinal fluid by aspiration and the intravenous infusion of glucose solutions free from, or too low in, sodium chloride, often leads to a low sodium syndrome though renal function seems adequate as judged by ample urine output.[21, 22] In fact, even the subcutaneous infusion of glucose solutions may cause marked temporary depletion of extracellular electrolyte by diversion into the glucose solution prior to its absorption.[4, 23] Fortunately, this type of low sodium syndrome is rapidly reversible as soon as the subcutaneous fluid is reabsorbed and the kidney can separate the water from the sodium.

The clinical features of the low sodium syndrome are compounded of symptoms and signs derived from the major systems of the body—primarily, the cardiovascular, gastrointestinal and neuromuscular systems, and the kidneys. A list (Table II) of the typical symptoms includes weakness, apathy, drowsiness, confusion, anorexia, nausea and vomiting, muscular cramps, faintness, and signs of circulatory and renal insufficiency leading to a mixture of "medical shock" and uremia. Thirst is usually absent after the full development of the syndrome, but may be marked early.

It is obvious that there is little specificity about most of these symptoms. The age of the patient, the presence of vascular changes in the brain, heart or kidneys, and the rate of development of the electrolyte depletion and secondary dilution markedly influence the severity of the clinical syndrome and the type of predominant expression. Therefore, it may be difficult to recognize the low sodium syndrome when it masquerades as an incomplete or atypical cerebral vascular episode, as a toxic psychosis, or as impending uremia in individuals who have some organic basis for these conditions.

The serum or extracellular chemical pattern found in the low sodium syndrome is constant in only one respect—a decreased concentration of sodium, usually a reduction of 15-20 m.eq./liter. Ordinarily the serum chloride and bicarbonate, or CO_2, concentrations are proportionally reduced. However, this relationship may be strikingly modified by the etiologic factor. For example, in cardiac patients after excessive mercurialization, a disproportionately lower serum chloride and higher serum CO_2, with alkalosis, may be found unless ammonium chloride has been given freely.[24, 25] On the other hand, the severe renal impairment and metabolic acidosis secondary to a prolonged low sodium syndrome may lower the serum bicarbonate disproportionately. Changes in the serum potassium concentration may occur in either direction. The role of intracellular potassium depletion in the etiology of the clinical syndrome is difficult to assess without further controlled experiments on treatment with potassium salts alone. However, potassium depletion can aggravate the condition of the cardiac with a low sodium syndrome by increasing the likelihood of digitalis toxicity,[26] secondary myocardial insufficiency, retention of water and further dilution of sodium. The proper use of potassium may be vital in such cases.

Increases in blood urea nitrogen, non-protein nitrogen and creatinine usually occur rapidly in the course of the full-blown low sodium syndrome and in severe cases attain uremic levels.[3, 19, 20] However, the degree of non-protein nitrogen retention may be mitigated by liberal infusion of glucose solution to produce diuresis and exert a sparing effect on nitrogen catabolism. The absence of gross non-protein nitrogen retention cannot, therefore, always be used as evidence against the existence of a low sodium syndrome.

The urine is ordinarily sharply reduced in volume but may be concentrated or dilute, depending on the underlying disease, the duration of

TABLE III—EXPERIMENTAL LOW SODIUM SYNDROME

1. Peritoneal Dialysis with Glucose Solutions.
2. Low Sodium Diet and Thermal Sweating.
3. High Water Intake during Work in Hot Environment.
4. Low Sodium Diet, Intravenous Glucose and G-I Aspiration.
5. Massive Hypodermoclysis with Glucose Solutions.
6. Low Sodium Diet and Mercurial Diuretics.
7. Adrenalectomy and Hydration.
8. Removal of Ascitic Fluid on Low Salt Diets.
9. Low Sodium Diet and Cation Exchange Resins.
10. Pyloric Obstruction and Intravenous Glucose.

the syndrome, and other factors.[1-3, 21] Thus, in Addison's disease or in the salt-losing stage of chronic renal disease or acute toxic nephrosis, the continual escape of salt will give rise to the dilute urine of an osmotic saline diuresis. On the other hand, in the early shock-like phase of acute sodium depletion due to paracentesis and other causes of extrarenal loss of sodium, the urine may be highly concentrated as though pituitary ADH (antidiuretic hormone) were acting powerfully on the distal tubule. In these cases and in heart failure over-treated by low salt diet and mercurials, sodium and even chloride may virtually disappear from the urine. This is probably a reflection of reduced glomerular filtration rate and renal plasma flow, of glomerulo-tubular imbalance and, most important, of the activity of adrenal cortical salt-retaining hormones on the renal tubule. Urinary potassium excretion ordinarily continues at a normal or increased rate but may be reduced as renal impairment progresses. The serum potassium level may then rise as the resultant of increased cellular release of K and decreased excretion.

The physiologic disturbances arising from sodium depletion in excess of water loss or in the presence of water retention, have been critically investigated in the classic experiments (Table III) of Kerpel-Fronius,[27] Darrow and Yannet,[28] McCance et al.,[1,2] Nadal et al.,[21] Danowski,[4,6] Elkinton et al.[5, 7, 29, 30] Essentially, low extracellular sodium is promptly followed by shift of water from extracellular to intracellular space, causing decrease of extracellular fluid, overhydration of cells, alterations in thirst and diuresis, the general and local hemodynamic disturbances and, probably, important changes in cellular metabolic reactions. If water is

available it is avidly retained and, by its dilution of body electrolytes and other effects, probably plays a major role in the low sodium syndrome.

In both the clinical and experimental low sodium state certain things stand out—impaired water diuresis, decreased excretion of sodium in urine, sweat, saliva and gastrointestinal secretions,[2, 10] early decrease in cardiac output with little fall in blood pressure,[31] reduction in renal blood flow and glomerular filtration rate, increased tubular reabsorption of sodium and refractoriness to mercurial diuretics.[24, 32] Some of these changes point to increased ADH secretion and increased output of adrenal cortical salt-retaining hormones. Obviously, the combined effect is to promote sodium and water retention; apparently, to preserve the volume of extracellular fluids.[33] Since sodium is usually not available and water always is in free supply, excessive water retention occurs in relation to sodium and causes dilution of body sodium. Depletion and dilution are, in this sense, inseparable in the low sodium syndrome.

The intimate cellular metabolic disturbances arising from cellular overhydration, from cellular depletion or shifts of sodium and potassium, and associated changes, are largely unknown; but they are undoubtedly reflected in the deterioration of function of the myocardium, kidneys, brain, muscles and other organs and tissues.[29] In short, the low sodium syndrome is not simply renal insufficiency, as some have assumed. All of this physiologic disorganization can be reproduced in the normal animal or human subject. Is it any wonder that when it develops in the patient with congestive heart failure or cirrhosis of the liver, it can easily lead to a fatal outcome? Hence, the importance of prevention, of early recognition, and a definitive treatment.

It should be noted that the low sodium syndrome arises often in patients with relatively little edema. As long as there is considerable edema fluid that is being mobilized by effective diuresis, there is less danger of impairing the circulation by sodium depletion. This is especially true in the edematous cirrhotic patient with ascites who, after each paracentesis, can reabsorb the peripheral edema fluid to refill the peritoneal cavity, thereby avoiding depletion of the "active" extracellular fluid.[11] But in edematous cardiacs who happen to have a very poor circulation, or hypoalbuminemia, the edema may be relatively segregated and unabsorbable. In such patients, a low sodium syndrome will result more readily from the usual causes because the mechanisms for water retention will be hyperfunctioning. Finally, in hypertensive and arterio-

sclerotic individuals, urinary sodium loss may continue in spite of a low serum sodium because the renal tubules are impaired in their reabsorptive function, and will not be able to respond adequately to the sodium conserving mechanisms. Even small daily urinary losses will add up, in time, to a considerable deficit and hasten the onset of the low sodium syndrome. In these hypertensive patients, a high fluid intake, in the attempt to treat "uremia," may result in increased diuresis but at the expense of further sodium wastage and its deleterious consequences.

The basic mechanisms regulating the body fluid balance during the low sodium syndrome are, apparently, the same volume-controlling mechanisms as operate so efficiently in the normal subject to compensate for transient dehydration,[33] for changes in posture[34-36] or for expansion of circulating or extracellular volume.[35, 37-39] The evidence for volume controlling receptors is derived from a variety of experiments. Thus. expansion of plasma volume with iso-oncotic (4 per cent) human serum albumin leads to water diuresis and maintained electrolyte excretion.[38] Expansion of extracellular volume by infusion of hypotonic salt solutions produces a significant increase in urinary sodium and water output in spite of dilution of the serum sodium.[35] This natriuresis is apparently not mediated through adrenal cortical discharge, although maintenance doses of adrenal cortical hormones are necessary for this response in adrenalectomized animals and in patients with Addison's disease.[40] Contraction of extracellular volume in the cephalad region, as produced by the upright posture,[34] tilting to the head-up position,[36] venous obstruction in the lower part of the body,[41] or reduction of cardiac output by venesection[42] or acute digitalization[43] in normal subjects, regularly leads to sharp decrease in urinary salt excretion, presumably as result of stimulation of volume receptors or some other type of circulatory-sensitive structures in the head. On the other hand, an ingenious series of experiments[34,42] with external compression of the veins in the neck in the sitting subject has demonstrated a prompt increase in urinary sodium excretion as a result of intracranial congestion. This is a reversal of the normal response in this position. It is significant that the patient with congestive heart failure does not react to the stimulus of compression of the neck with an increase in urinary salt output.[44] On the contrary, the volume controlling mechanisms in the edematous cardiac seem to act in the direction of continual expansion of volume and renal retention of salt.[8,9,33,44] The precise reason for this abnormal behavior is unknown.

It may be related to some deficiency on the arterial side of the circulation to a sensitive cephalad region.[45]

Volume regulation under certain circumstances takes precedence over the hypothalamic osmoreceptors that control extracellular electrolyte concentration. Thus, in the low sodium syndrome water will be retained, to maintain volume, in spite of further dilution of electrolytes in an already hypotonic extracellular fluid. Here, ADH secretion is apparently increased instead of being shut off. The resulting marked impairment of water diuresis may actually cause increased edema in cardiac patients with hyponatremia. The stimulus for the excessive ADH production must somehow be related to reduction in actively or effectively circulating volume to the sensitive cephalad region. A physiologic compromise must be achieved between two important homeostatic mechanisms—one for the maintenance of effective circulating volume, and the other for the preservation of extracellular sodium concentration. For this choice, under stress, the body must pay a price!

As we have seen, the processes of depletion and dilution are intimately combined in the low sodium syndrome. In all the clinical and experimental states associated with this syndrome, impaired water diuresis is a constant and striking phenomenon.[12, 33] It has often been attributed, on more or less evidence, to increased ADH activity. This association between retention of water and ADH activity brings to mind the numerous studies on impaired water diuresis and water retention in cirrhosis with ascites,[10, 46-49] in nephrotic edema,[50] and in congestive heart failure.[48, 51, 52] In all of these edemas, particularly after some attempt at treatment, the serum sodium is often diminished. More important, however, in patients with congestive heart failure situations of acute hyponatremia may develop during acute infections, over- or under-digitalization and other stresses, along with unmistakable signs of retention of water and increased heart failure.[9] This is, primarily, a dilution hyponatremia, in contrast to the low sodium syndrome initiated by depletion. The external balance of sodium is unchanged and the administration of hypertonic saline is not beneficial.

That the dilution syndrome is related to increased ADH secretion under conditions of stress is strongly suggested by the water diuresis and spontaneous return of serum sodium to normal levels as the patient recovers from the acute episode with improvement of his cardiac failure. Furthermore, the entire sodium dilution syndrome can be reproduced

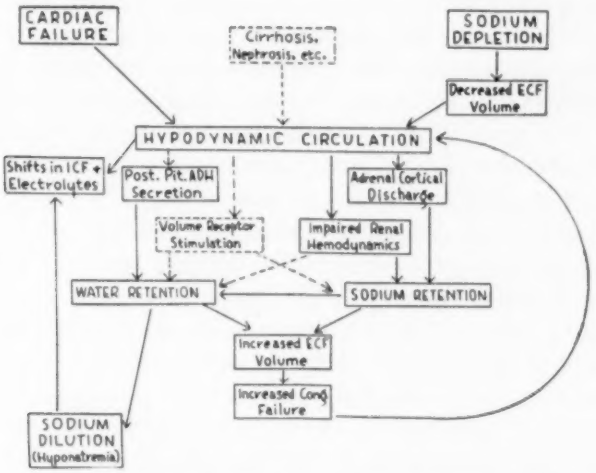

Fig. 1: This is a schematic representation of the physiologic disturbances involved in the low sodium syndrome whether the result of sodium depletion or sodium dilution. The dotted lines indicate hypothetical processes for which there is incomplete evidence. This diagram omits a number of intervening mechanisms.

in the patient by the appropriate administration of Pitressin Tannate in Oil, to mimic the increased endogenous ADH discharge.[8,52] Obvious requirements for this experiment are a low salt intake and an adequate supply of water. When the Pitressin is withheld, the sequence is completely reversed—water pours out in the urine, signs of congestion recede, the weight falls and the serum sodium rises rapidly.

The dilution syndrome and the sodium depletion syndrome have much in common clinically. They both lead to increasing circulatory failure (Fig. 1)—in the form of medical shock in non-edematous patients with sodium depletion, as congestive failure in edematous patients if fluids are pushed. The association of hyponatremia, increasing edema and marked azotemia in cardiac patients, on a low salt diet, receiving frequent mercurials and on a free fluid intake, should facilitate the diagnosis of combined sodium depletion and sodium dilution syndromes.[20]

Certain practical therapeutic problems arise in the low sodium syndrome, some of which are easily handled, others only with great difficulty. Thus, it is a simple matter to correct sodium depletion in a medical or surgical case without cardiac, renal or hepatic edema. Hypertonic

salt solution, balanced as to anions if necessary, is given in an amount calculated to remedy the sodium deficiency on a total body water basis:[14] First, because of osmotic dilution of added sodium by all the body water; second, because cellular sodium may also have been depleted. Usually, only one-third to one-half of the calculated amount is given in the first infusion and the rest at intervals depending on the clinical response. The effects are generally both dramatic and gratifying; in fact, among the most triumphant therapeutic results.

Major difficulties arise in treating the low sodium syndrome in edematous patients. Here, in the first place, there arises the question: How much depletion of sodium and how much dilution? Secondly, since sodium and water excretion are markedly impaired in all edematous states, one must worry about the ultimate effects of the net retention of the extra salt administered. Third, the estimate of total body water as a percentage of weight must be adjusted upward considerably to take the amount of edema into account. Fourth, there is always the possibility in the cardiac failure patient that increased pulmonary congestion and edema may eventuate during the infusion, especially if digitalization has not been adequate, or excessive, and if tissue potassium depletion is present. It is vital to the success of the treatment that the patient's fluid intake be sharply restricted during and for some hours after the infusion, which should be much slower than in the non-cardiac. Supplements of potassium and calcium may be required.

What should the physician do when he is uncertain as to the proportion of sodium depletion and sodium dilution in an edematous patient who does not show the classical symptoms of sodium depletion? In such cases, it is best to treat the patient expectantly without saline unless the serum sodium is very low—120-115 m.eq./liter or less—or there has been a rapid fall in serum sodium without gain in weight. At these extremely reduced extracellular levels of sodium, it is possible that the cellular metabolism may be damaged by the low sodium concentration, per se, or by the abnormal cation ratios. Furthermore, a slight further depletion, by diarrhea, vomiting, sweating, etc., might be disastrous. Therefore, one must take the risk of adding to the patient's total salt load and edema by administering at least enough hypertonic saline to elevate the serum sodium 5 to 10 m.eq./liter. If the response is good, further elevation of serum sodium can be effected. It is true, however, that the exact knowledge required for accurate clinical judgment is still

lacking and, for the present, one must proceed empirically and accumulate observations under controlled conditions.

In summary, the low sodium syndrome is a complex clinical and physiological disturbance, in which the factors of sodium depletion and water retention are closely interrelated. The control of effectively circulating volume, on the one hand, and of body electrolyte concentration, on the other hand, may result in a conflict in regulation and lead to a physiologic compromise in which water must be retained in spite of further dilution of the low extracellular sodium concentration. In patients with congestive heart failure, certain situations may lead to increased antidiuretic hormone secretion, retention of water and dilution of sodium. The resulting increased failure of the circulation in this dilution syndrome has much in common with the circulatory insufficiency of the sodium depletion syndrome. Treatment must be based on an accurate evaluation of the relative roles of sodium depletion and dilution.

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POTASSIUM IMBALANCE*

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POTASSIUM metabolism is primarily the metabolism of intracellular electrolyte. This immediately poses a handicap in the study of discrete mechanisms—not only in experimental work—but even more so in clinical disorders. For while extracellular fluid may be sampled directly, the fluid of the cell defies such direct analysis, and, most often, must be studied in terms of what's left over on the outside—namely the plasma concentration. In addition, while extracellular fluid is quite homogeneous, intracellular fluid probably has as many functional patterns as there are different types of cells. Thus, although it is extremely convenient and useful to speak of the "intracellular fluid compartment," it may not be improper to remind ourselves that this phrase represents one of the greatest oversimplifications of modern physiology. To complicate matters further, it is often the wide variations in external balance which are of greatest immediate interest, and it is from these fluctuations that one often attempts to extrapolate backwards to read some meaning into the behavior of distant cells. And lastly, it is frequently the case that it is not the basic behavior of a given tissue that is of apparent importance, but rather the small nudge which it receives from the endocrine glands.

It is also proper that we distinguish between two general problems of potassium metabolism—first, those functions of the cell which directly influence the distribution of potassium within the organism, and secondly, the effects of given concentrations of potassium upon various body functions, especially those of the neuro-muscular system. It is with the first set of problems that we will be mainly concerned this evening.

Let us consider the distribution of potassium in the body. Table I represents some data compiled from different sources in the literature.[1-3] Although I have taken liberties with some of the calculations, I think, in

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TABLE I—POTASSIUM AND SODIUM CONTENT OF VARIOUS ORGANS OF MAN

Values are subject to considerable variation, especially in association with alterations in content of fat. Calculated from references cited in text.

	Weight *kg*	*K* *mEq*	*Na* *mEq*
Whole body	70	3,800	5,100
Skeletal muscle	30	2,730	810
Skin	18	360	1,600
Erythrocytes	2.4	252	36
Bone	12	218	1,600
Brain	1.9	150	133
Liver	1.8	135	74
Heart	0.3	24	11
Kidneys	0.3	18	22
Plasma	2.6	12	363

general, that the picture presented is reasonably correct. Several points may be emphasized. First, the recent studies of McCance indicate that there is almost as much potassium as sodium in the body, and second, that the major depot of potassium is skeletal muscle. Although the data on bone are somewhat meager they may be mentioned in order to point out the possible role that tissues of this type may have as a reservoir for potassium as well as for sodium.[3]

With the introduction of isotopes into the study of biochemical processes it has become apparent that the potassium of the cell is in the dynamic state and that it readily exchanges with that of the extracellular fluid. In Figure 1 these exchange reactions are shown very diagrammatically and emphasize the differences in the behavior of different tissues. These data are taken from the work of the groups at Rochester[4] and at Tulane,[5] and represent analyses of tissues removed at intervals of time after the administration of isotopic potassium. In general, there is a rough correlation between tissue metabolism and the rapidity of electrolyte exchange. Note that skeletal muscle is intermediate, while bone is probably very slow in its rate of turnover. The anomalous behavior of kidney does not reveal a peculiar cellular function of that organ, but rather, as has been shown by Bradley's group,[6] is probably a manifestation of the

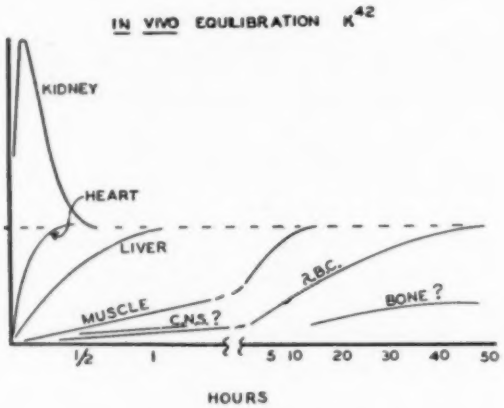

Figure 1. Equilibration of isotopic potassium in different tissues. Data from in vitro experiments.[4,5] Very schematic. Broken line denotes complete equilibration of tissue potassium with plasma potassium. Unconfirmed values are indicated by question marks.

length of time required for the fluid filtered at the glomerulus to travel through the tubular system into the pelvis and ureters.

Potassium imbalance, by definition, is to be considered as an abnormal concentration of potassium in the body as a whole, or in any specific fluid or tissue, and will result either from an imbalance between external intake and output or from internal readjustments. In a general way, depletion is most commonly the result of decreased dietary intake, coupled with exceptional losses through the gastrointestinal tract and the kidney. In terms of overall balance, we may summarize the situation very briefly. All gastrointestinal secretions—whether from the stomach, biliary tract, pancreas, small or large intestines—contain potassium, and although the concentration is subject to very great variation, as a very conservative estimate we may use the figure of 8-10 mEq/liter, or roughly twice that of the plasma.[7] It is probably impossible to lose gastrointestinal secretions without losing potassium. We will consider some intrinsic renal mechanisms later, but in general we may note that renal conservation of potassium is usually not very efficient. Whereas restriction of sodium leads to the virtual disappearance of this ion from the urine, persistent losses of potassium, up to 20 or 30 mEq per day, are noted in the face

of severe depletion, and may be accentuated by trauma or other metabolic demands which sound the bells for the "alarm reaction."[8] Although potassium depletion is a fairly common problem, excessive retention is relatively rare and is most frequently seen in the anuric phase of acute renal insufficiency or in the advanced stages of chronic kidney disease. The diminished renal excretion of potassium is, of course, the major factor, but the degree of the resultant hyperkalemia is quite variable and in many cases is a reflection of the severity of associated tissue damage.

Let us briefly consider the techniques which are available for the evaluation of potassium balance. 1) *Serum Level.* It has become obvious that in many circumstances the level of potassium in the serum is an inaccurate measure of intracellular changes or of total balance. Granted that potassium depletion is usually associated with hypokalemia, the size of the intracellular deficit cannot be determined simply by measuring the plasma concentration. For example, intracellular deficits may progress markedly during the course of various abnormal conditions while, at the same time, the degree of hypokalemia may fluctuate only slightly. Furthermore, low serum levels are observed in both familial periodic paralysis and in chronic metabolic alkalosis; yet in the first condition there is no evidence of a cellular loss of potassium, while in the latter negative balances with cellular depletion are the rule. Although the serum concentration may be of paramount importance in determining the immediate clinical picture, especially as reflected in the function of skeletal and cardiac muscle, it must again be emphasized that the serum level alone can not be used to estimate the magnitude of the total deficit. 2) *Tissue Analysis.* Valuable information has been obtained from direct chemical analyses of tissues, especially muscle biopsies, but this is hardly a procedure for routine use. The red blood cell is more accessible for direct analysis, and although abnormalities have been found by this method, it is probable that the potassium concentration in the erythrocyte does not necessarily reflect the status in other tissues. 3) *Balances.* Many balance studies have been reported with calculations of intracellular changes as the difference between extracellular balance and total external balance, the former being estimated by the distribution of a reference substance, usually chloride.[9] Although too laborious for routine use, this technique has yielded consistent results which are probably valid when there are relatively enormous changes in external balance so

that the unknown variables which are inherent in the calculation become relatively unimportant. 4) *Isotope Dilution.* In recent years the total exchangeable potassium of the body has been determined by the isotope dilution technique. In normals rather consistent values have been obtained—approximately 45 mEq/kg. in men.[10, 11] This may be somewhat less than the amount found in direct chemical analyses,[2] suggesting the possibility that there are some body stores exchanging at a very slow rate. However, accurate comparisons are not possible because of variations in body fat. In a small number of studies the changes in exchangeable potassium have agreed quite closely with values from simultaneous balances. In terms of convenience the isotope dilution technique has much to recommend it, but whether it will be clinically useful or essential remains to be determined. 5) *Potassium Loads.* Attempts to appraise potassium imbalance have been made by administering loads of potassium salts, and calculating the amount retained from that excreted in the urine.[12, 13] Although the results appear reasonable, the presence of hyperkalemia is an obvious contraindication, and the test is not simply a measure of cellular stores, but inherently is also a measure of renal function. 6) *Electrocardiogram.* And lastly, the electrocardiogram must be considered as a useful adjunct for clinical evaluation. In general, the electrocardiographic changes parallel fluctuations in the serum concentration of potassium, but the many exceptions which have been observed make a precise correlation impossible. It may be noted, that when the problem is one of hyperkalemia, chemical analyses of potassium are of less immediate importance than the electrocardiographic changes since these directly reflect an abnormality threatening the life of the patient.

An almost endless number of factors has been described which, in one way or another, might determine the distribution of potassium within the body. In an attempt to discuss the common clinical abnormalities in terms of underlying mechanisms, I would like to consider three major factors—first, certain metabolic functions of individual cells, secondly, the effects of hydration and dehydration, and, thirdly, alterations in acid-base balance. This is done with the realization that this subdivision may be quite artificial, but more important, with full knowledge that many of the correlations proposed are at times based on evidence most charitably described as indirect.

The role of cellular metabolism may be considered first because an increasing number of studies indicates that the basic processes of cellular

accumulation are accomplished by specific transport mechanisms. Studies of these reactions are being actively pursued in many laboratories, and as an example of the type of result which may be obtained by in vitro techniques, I would like to mention some of our experiments on kidney slices.[14,15] We have worked with slices whose potassium concentration was artificially lowered by washing in chilled solutions of sodium chloride. We then examined their behavior to determine those conditions under which a normal intracellular concentration of potassium could be re-established during incubation in Warburg vessels; this permitted measurement of simultaneous respiratory activity. It was found that the accumulation of potassium from a low external concentration required active aerobic oxidation. Electrolyte transport was depressed by a variety of metabolic inhibitors, and specific inhibition was noted by agents which uncoupled aerobic phosphorylation. From studies of this type it has become apparent that potassium accumulation is in some way dependent upon the energy derived from aerobic oxidation in a number of tissues—kidney, liver[16] and brain[17]—while anaerobic glycolysis is implicated as the driving force in the erythrocyte.[18]

A schematic presentation of another phenomenon is shown in Figure 2. Two reactions occur in the inhibited or injured cell. First, potassium fails to accumulate and is replaced by sodium, thus maintaining electrolyte neutrality and osmotic equilibrium. But, in addition, a second reaction also can be observed. The inhibited cell swells with water, and this swelling is associated with the influx of extracellular electrolyte (that is, sodium) thus maintaining the cell in approximate osmotic equilibrium. It is to be noted that this means that the hydration of a given cell is not simply the result of the prevailing osmotic pressure, but is also, in part, directly determined by metabolic reactions.

One may well wonder to what extent these reactions may be clinically applicable. By the in vitro techniques, extremes of environmental conditions are examined—i.e., incubation in 100 per cent oxygen or 100 per cent nitrogen. Possibly qualitatively similar changes, but of much smaller degree, are to be found in disease states. One such clinical counterpart has been well studied—namely traumatic shock. The tissue analyses obtained by Fox and Baer[19] on experimental shock are almost identical to the "inhibited cell" depicted in Figure 2, and the changes are likewise reflected in the hyperkalemia reported in some cases of severe shock. It remains to be seen whether or not less severe disturbances

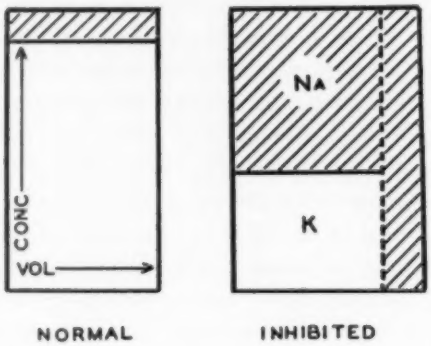

Figure 2. Electrolyte and water composition of normal and inhibited cell (schematic). Depression of metabolic activity produces a loss of potassium with a corresponding increase of sodium. The additional gain of water and sodium varies with the nature of the metabolic inhibition, but the calculated osmotic pressure remains approximately constant.

of cell metabolism—such as might result from anoxia, fever, uremia or the nebulous "toxemia" of infection—whether these are capable of evoking similar but lesser responses. Such a possibility is certainly suggested by the increasing number of reports in which serum sodium falls for unexplained reasons—presumably because it has disappeared into cells. A somewhat unusual example of abnormal cellular metabolism is seen in sickle cell anemia. Tosteson[20] has shown that the high serum potassium exhibited by some of these patients can be correlated with a specific defect in the potassium transport of the abnormal erythrocytes.

I should next like to consider some of the changes in potassium distribution which occur when alterations in water metabolism are the primary event. It has now been abundantly demonstrated that cellular dehydration—whether produced by restriction of water intake, infusion of hypertonic solutions, or by abnormal losses through the kidney or gastrointestinal tract—that dehydration, in presence of normal renal function, leads to a loss of potassium in excess of the amount contributed by the simultaneous loss of nitrogen.[21]

When rehydration is accomplished by the administration of extracellular electrolyte and water (i.e. saline) not only does the extracellular volume expand, but the cells themselves take on water, which dilutes

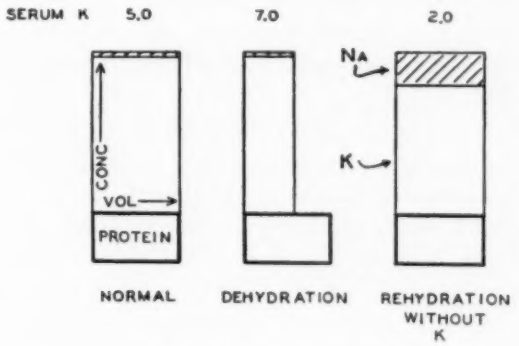

Figure 3. Effects of dehydration on cellular composition (schematic). A constant amount of cell protein is used as a reference point and is drawn on an arbitrary scale. Changes in water volume are greatly exaggerated, but are in the direction of well documented abnormalities. For simplicity the total concentration of cellular cations is shown as constant, but small to moderate variations undoubtedly occur. For discussion see text.

the intracellular electrolyte. In the interests of osmotic equilibration, this deficit is at least partly compensated for by the migration of sodium into cells. These changes are shown in very schematic form in Figure 3. Although potassium depletion, in terms of overall *balance*, exists at the height of dehydration, this may not become apparent in terms of potassium *concentration* until rehydration has been accomplished.

It may seem anomalous to take diabetic acidosis as our clinical example of dehydration since so many other factors are involved as well. However, let us consider first the potassium disturbance that occurs during the development of acidosis, and then the problems which arise during its correction. The careful balance studies of Atchley[22] and of Butler[23] and their respective associates have shown that the fairly mild acidosis which develops upon the experimental withdrawal of insulin is associated with a marked loss of potassium. The results from the two studies, recalculated on the basis of the hypothetical 70 kg. man, show the average losses to be: weight, 4.3 kg.; sodium, 240 mEq; chloride, 144 mEq; potassium, 380 mEq; phosphate 4.4 gm.; and nitrogen, 42 gm. Note that the potassium loss far exceeds that of sodium; it is likewise proportionally greater than the nitrogen loss, and thus can not all be attributed

to tissue breakdown. It is probably greater than the loss which may be anticipated from the disappearance of a reasonable amount of liver glycogen. It therefore conforms to the pattern described above for simple dehydration.

Although these data have often been cited as an example of potassium excretion in compensation for acidosis, it is not at all certain that such is the case since almost all examples of acidosis are complicated by dehydration. We know that dehydration without acidosis leads to potassium loss, and we may well ask if acidosis per se does the same. Darrow's group[24] have analyzed skeletal muscle in both metabolic and respiratory acidosis and find, if anything, an increased potassium content. Berliner[25] has attempted to study the renal response to acute acidosis, in the absence of complicating changes in urine volume or hydration, by infusing neutral phosphate and then switching to the acid salt. He noted only minimal changes in potassium excretion, and these in the direction of increased conservation. Taken all in all, there is no direct evidence that acidosis per se leads to a marked potassium deficit. I am therefore tempted to attribute the loss in diabetic acidosis to dehydration—at least till the end of this talk.

Interest in the disturbances developing during the treatment of diabetic acidosis dates from the reports of Holler[26] and of Frenkel, Groen and Willebrands[27] who observed that the marked disturbances of neuromuscular function, which developed during the course of treatment, were associated with severe hypokalemia, and were relieved by the administration of potassium. There have been many subsequent reports on the metabolism of potassium during the treatment phase of diabetic acidosis. The average serum concentration on admission to the hospital is about 7.0 mEq/l. This high value is undoubtedly a reflection of cellular loss in the presence of failing renal function. Following treatment with insulin and sodium chloride infusions (and in many cases with glucose) the serum potassium level drops promptly so that the level at eight hours after the start of therapy is between 3 and 4 mEq/l., with many values as low as 2 mEq/l. At least four factors contribute to the development of the hypokalemia—dilution due to expansion of plasma volume, continued renal loss (probably accentuated by the administration of excessive amounts of sodium chloride), deposition with glycogen in the liver, and an uptake by other cells. The exact contribution of each factor is probably quite variable and can not be accurately evaluated.

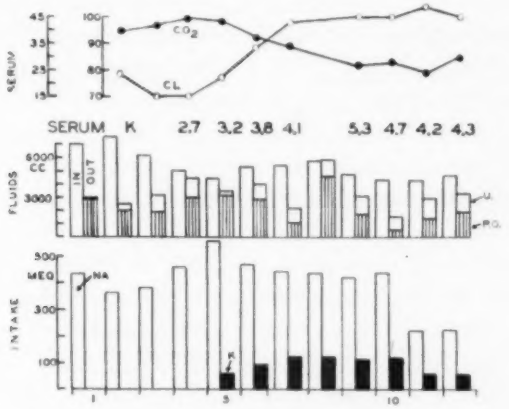

Figure 4. Correction of metabolic alkalosis by administration of potassium chloride. Diagnosis—primary carcinoma of duodenum. Time is given in days. All serum values are in mEq/l; scale for CO_2 is to the left of that for chloride. Infusions of isotonic sodium chloride maintained an adequate fluid balance but were without effect on the alkalosis, which was promptly corrected by the administration of potassium chloride in addition.

Brief mention has already been made of potassium excretion in acidosis, and now let us consider the relationship of the potassium ion to alkalosis—especially metabolic alkalosis. The first indication of such a relationship was observed by McQuarrie, Johnson and Ziegler in 1937[28] when they studied a patient with Cushing's syndrome exhibiting alkalosis and hypokalemia. The alkalosis was resistant to treatment with relatively enormous amounts of sodium chloride but was quite rapidly corrected by the administration of reasonable quantities of potassium chloride. Since then, there have been many reports on the role of potassium in the correction of alkalosis.

Two examples may be cited to emphasize the clinical importance of the problem. We had an opportunity to observe two patients with a somewhat rare condition—a primary carcinoma of the duodenum with almost complete intestinal obstruction. Both vomited tremendous amounts of fluid—up to 6 liters per day. The first patient had a negligible intake of potassium and received virtually no electrolyte parenterally

except sodium chloride—and this in rather large amounts—on some days up to 1000 mEq. On this regimen he exhibited persistent hypokalemia; muscle biopsy showed a low potassium concentration with high intracellular sodium.[29] Alkalosis persisted for six weeks despite the so-called heroic parenteral therapy with sodium chloride. The second patient (Figure 4) had an identical clinical picture. After a control period of parenteral sodium therapy, he received potassium chloride. Serum bicarbonate fell, chloride rose, and the alkalosis was rapidly corrected. Many similar cases are to be found in the literature.

Briefly stated—alkalosis tends to beget potassium depletion—and potassium loss tends to result in alkalosis. The mechanisms involved are probably so intertwined that an arbitrary classification of the etiological factors may not be completely justified. Nevertheless, the important conditions may be summarized as follows: *Primary Alkalosis* (with demonstrated loss of potassium)—alkali administration, vomiting acid gastric juice, hyperventilation, and diarrhea with congenital defect in chloride absorption; *Primary Potassium Deficit* (with demonstrated alkalosis)—no dietary intake of potassium, excessive administration of adrenal steroids, Cushing's syndrome, removal (by suction, etc.) of contents of the gastrointestinal tract, and the malabsorption syndromes.

Before considering the possible mechanisms leading to potassium depletion and alkalosis it may be well to emphasize that this relationship is not an inevitable one. Two examples will suffice. *First,* Fourman, in a controlled study,[30] ingested an acid-loaded ion exchange resin which produced a very negative potassium balance. At the same time, he developed a rather severe *acidosis* due to the absorption of acid from the resin. *Secondly*, we studied three patients with acidosis due to an impairment of the base sparing mechanisms of the kidney.[29] In the presence of abnormal renal function, potassium was lost as a compensatory mechanism, and depletion resulted, as indicated by a low concentration in both serum and muscle. It may be pointed out that in both of these examples we are apparently dealing with dual disturbances—the negative potassium balance itself *and* the unusual types of acidosis, due, in the first instance, to absorption of hydrogen ions from the resin, and in the second instance, to the failure of normal renal mechanisms.

Attempts to explain the relationship between potassium depletion and alkalosis have been focused on two types of compensatory reactions—those of the kidney and those of the skeletal muscle. Before considering

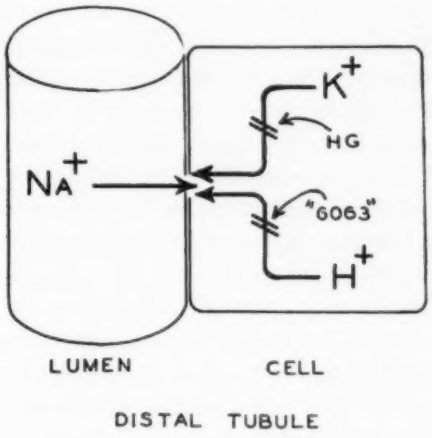

Figure 5. Renal cation exchange mechanism of distal tubule, as proposed by Berliner et al.[33] For discussion see text.

them in detail, it may be emphasized that to a certain extent both factors must play a role in defining the final result.

The renal mechanisms of potassium excretion are unusual in that the tubules are capable of transporting this ion in both directions—that is, filtered potassium is reabsorbed but secretion into the tubular lumen also occurs.[31, 32] Admittedly, such a two-way reaction defies precise analysis in clinical problems. However, the many experimental correlations that have been obtained justify the belief that the secretory process is an active determinant in the control of net excretion. This implies that potassium reabsorption is virtually complete and that variations in reabsorption contribute but little as a regulatory mechanism. It is likewise reasonable to presume that secretion occurs in the distal tubule. It has been shown that the net reaction of potassium secretion is one of cation exchange—that is, a potassium ion from the tubular cells exchanges with a sodium ion from the lumen of the tubule. Berliner and his group[33] have proposed the mechanism depicted in Figure 5, based on the following observations. When large amounts of potassium appear in the urine, the pH tends to rise—and this holds true no matter by what means excretion is acutely increased, that is by the administration of potassium salts or

by the action of "6063," a powerful inhibitor of carbonic anhydrase. It had previously been shown by Pitts[34] that the acidification of the urine is accomplished by the tubular secretion of hydrogen ions in exchange for sodium. An alkaline urine indicates a *decreased* secretion of hydrogen ion, and a urine high in potassium is due to *increased* potassium secretion. The coexistence of *decreased* hydrogen secretion and *increased* potassium secretion can, under these circumstances, be taken as evidence of competition between these two ions for that secretory mechanism which permits exchange with sodium. This mechanism is more definitely demonstrated by the action of two drugs—mercurial diuretics and "6063." The latter blocks secretion of hydrogen ions and causes a marked increase in potassium output, but the simultaneous administration of mercury blocks the augmentation of potassium secretion while the effect of "6063" on acidification is unchanged. The simplest interpretation of these experiments is as follows: The distal tubule has a cation exchange mechanism whereby sodium from the tubular lumen exchanges with either hydrogen or potassium, which to a certain extent compete with each other, but which also have distinct and separate mechanisms as indicated by the specific pharmacological blockade. It is probable that clear evidence of competition may only be obtained when the mechanism is loaded to maximal capacity. It should also be emphasized that the simultaneous secretion of smaller amounts of both potassium and hydrogen ions is not precluded by this scheme, nor is it to be assumed that both ions are necessarily secreted in equivalent amounts.

How, then, might such an exchange mechanism account for the relationship between alkalosis and potassium depletion? Other factors remaining constant, the result of changing the concentration of any by the three reactants would be as follows: If the hydrogen concentration in the cells were decreased, as in alkalosis, the opportunity for an exchange between potassium and sodium would be enhanced and potassium would be secreted and this would result in its depletion. On the other hand, if the primary event were potassium depletion, there would be a better chance for hydrogen to exchange with sodium and more fixed base would become available to combine with the bicarbonate of the body, and alkalosis would result. In a similar manner, a change in the sodium concentration of the distal tubule might be expected to influence potassium balance. Potassium deficits are often accentuated by the excessive administration of sodium especially by large infusions given for the

maintenance of patients with gastrointestinal disturbances. Although other renal mechanisms may be involved, increased potassium secretion would be anticipated from the equilibrium depicted here. In a similar way, experimental potassium depletion due to the administration of adrenal steroids does not develop when the sodium intake is low[35] and, indeed, is accentuated by a high sodium intake.*

A phenomenon possibly related to this exchange mechanism is the presence of an acid urine in cases of severe alkalosis of long duration. If the kidney is to serve as a useful organ in the regulation of the pH of the body, it should, under such circumstances, excrete an alkaline urine. The acid urine may well be a manifestation of potassium depletion which allows preferential exchange of hydrogen for sodium. Such an interpretation is in keeping with reported studies,[37, 38] although admittedly somewhat speculative in nature.

Let us now consider the other mechanism which has been proposed as the explanation for hypokalemic alkalosis. This involves a more general disturbance in cellular metabolism especially in the cells of skeletal muscle, and is based on two recently reported studies—that of Cooke and his associates from Darrow's laboratory[39] and that of Black and Milne from Manchester.[13] The latter observed the development of hypokalemic alkalosis in normal subjects depleted of potassium by restriction of intake, while Cooke's group correlated the changes in muscle composition with renal excretion during the correction of alkalosis in rats. Both groups reached essentially the same conclusion—namely that alkalosis secondary to a potassium deficit represented a compensation at the cellular level and was not mediated via the kidney. It is to be recalled that if the cation exchange mechanism of the renal tubule were responsible for the alkalosis secondary to potassium deficiency, then the development of alkalosis should be accompanied by an *increased* excretion of acid, and the correction of alkalosis by a *decreased* excretion of acid. However, the exact opposite was found to occur. Black noted a *decreased* excretion of acid during the development, and Cooke reported *increased* acidification of the urine as alkalosis was repaired. Both groups concluded that the alkalosis could not be explained by a renal mechanism and that it represented an altered equilibrium at the cellular level. Cooke calculated from his data that the equilibrium across the cell membrane of skeletal muscle is such

* Patients with congestive heart failure appear to have a low tolerance for potassium.[36] Although other factors can not be excluded, it is conceivable that these subjects are unable to increase potassium output in the urine because of their low rate of sodium excretion.

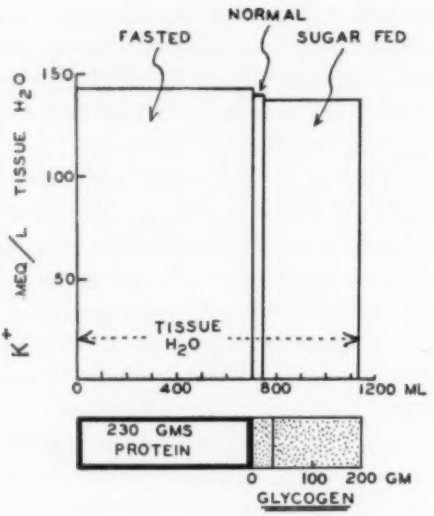

Figure 6. Effect of glycogen on potassium and water content of liver, from data of Fenn.[40] All values have been calculated with the protein of glycogen—free liver as a reference point. As glycogen is deposited it is accompanied by a parallel increase in water and potassium so that electrolyte (K) concentration remains almost constant, as does the ratio of tissue solids (protein plus glycogen) to tissue water.

that as three potassium ions are lost by the cell, they are replaced by two sodiums and one hydrogen. Potassium deficits therefore reduce the extracellular hydrogen ion concentration, or stated differently, increase the extracellular bicarbonate. It also follows that alkalosis of this type is essentially localized to the extracellular fluid, since the pH inside the cells will tend to fall even though buffered by intracellular anion.

The situation is obviously a complicated one and none of the proposed theories explain all of the observed relationships between potassium deficiency and alkalosis. Whereas crystal balls may have no place in scientific medicine, I would suggest that future studies may show that the renal mechanism may be of greater importance when alkalosis is the primary disturbance, while the cellular mechanism may be the major determinant with primary potassium deficits.

I would like to digress a moment and say a few words on the hepatic uptake of potassium. Fenn's studies[40] on the relationship of potassium to glycogen are depicted in Figure 6. All values have been calculated on the basis of the 230 gm. of protein present in a kilogram of glycogen-free liver. As the glycogen content was increased by varying the dietary intake of carbohydrate, tissue water increased with a proportional change in potassium, so that intracellular electrolyte concentration did not significantly change. Stated briefly, intracellular water increases in parallel with glycogen deposition. Parenthetically, this is in contrast to fat which is deposited without a water or electrolyte requirement. From Fenn's data, 2.7 mEq of potassium are taken up by the liver with each gram of glycogen. There is no evidence to suggest that the rate of glycogen deposition is limited by the availability of potassium. Fenn's results have often been quoted as showing that potassium accumulation depends on carbohydrate metabolism. This is true only to the extent that glycogen deposition represents a somewhat special event in the metabolism of sugar. The experiments actually may have a little bearing on the metabolic factors which maintain the normal concentration gradient.

These observations suggest a related subject – the treatment of hyperkalemia by the administration of glucose and insulin. While there is no doubt that this procedure will abruptly lower the serum level, it produces little more than transient benefit, since the subsequent utilization of the glycogen will be associated with a release of potassium.

Let us now consider a few of the problems encountered as manifestations of potassium imbalance. Varying degrees of asthenia, decreased intestinal peristalsis, cardiac dilatation (sometimes with hypotension) as well as the classical picture of severe paralysis – with or without respiratory embarrassment–are now well recognized as symptoms of potassium deficiency. An elevation of the serum concentration is also associated with disturbances in neuromuscular function, but most particularly with myocardial function as shown by abnormalities in conduction. Attempts to correlate these symptoms and signs with the plasma potassium concentration seem somewhat paradoxical because of the predominantly intracellular position of the ion. Although general trends have been noted, there are many exceptions – some of them quite striking – which prevent a precise correlation between symptoms and serum concentration. Important factors which may modify the picture include certainly

the serum calcium concentration, and probably the rapidity with which potassium imbalance develops. Since the electrical events associated with conduction in nervous tissue are attributed to the cation concentration gradients across the cell membrane, it would seem reasonable to believe that the clinical disturbances in neuromuscular function are not a simple consequence of the extracellular potassium concentration alone, but rather are reflections of the relative concentrations on either side of the membranes of the cells concerned.

And finally, a word about potassium as a therapeutic agent. There is universal agreement that it is best administered by the oral route, preferably in the form of beefsteak. But if parenteral therapy is necessary, it may be given by infusions containing up to 30 or 40 mEq per liter as the chloride salt. Although red blood cells contain large quantities of potassium, transfusions do not serve as a useful form of therapy; since it is hoped that the erythrocytes will remain intact, it follows that the potassium which they contain will not be available for other cells. At present the most common indication for parenteral potassium is the patient who is unable to eat and who must be maintained by parenteral alimentation for long periods of time. The daily requirement for most adults is probably somewhere in the neighborhood of 40 to 50 mEq. In the treatment of acute disturbances, at least in adult medicine,* parenteral therapy should *not* be directed towards the complete correction of the measured, calculated or imagined deficit, but rather it should be guided by the philosophy that the primary aim is to prevent a precipitous fall in serum concentration, such as may occur in the correction of diabetic acidosis. At present, this statement needs qualification only to the extent that potassium chloride is specifically required for the correction of those cases of metabolic alkalosis of long duration which are associated with severe potassium depletion. Indeed, when all the balances are calculated it is somewhat startling to realize that the greatest potassium imbalance of them all may well be the difference between the very large amount which the patient may have lost and the very small amount which he may actually need for the prevention or correction of symptoms.

* Potassium therapy is certainly indicated in the management of infantile diarrhea.[9] It is well known that adults tolerate acute episodes of dehydration much better than do infants. Even though a negative potassium balance may develop with gastrointestinal disorders, there is at present no evidence to indicate that the correction of the theoretical deficit is either necessary or desirable in the treatment of adults with such disturbances when of *short* duration.

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THE MANAGEMENT OF DIABETES

*Transcription of a Panel Meeting on Therapeutics**

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* Presented in the Monthly Panel Meeting Series, November 7, 1952 at The New York Academy of Medicine.
This transcription has not been edited by all the members of the panel.

MODERATOR ANDERSON: We have a rather distinguished, rather exceptional panel here, and I would like to emphasize one point. You notice that three of the four members are from outside of New York City. This has been no accident. We have had in the New York area a number of unfortunate ideologies as to therapy, and the feeling was that it would be well to bring in some talent from outside the city to clarify some of these points and principles. I hope that we can do so as we go along, and after I have introduced the speakers I shall try to say as little as possible.

At the far left is Dr. Garfield G. Duncan. Dr. Duncan is Clinical Professor of Medicine at Jefferson Medical College. To his right is Dr. Frank N. Allan, who is the current President of the American Diabetes Association, and Executive Director of the Medical Department at the Lahey Clinic. Next to him is Dr. Joseph T. Beardwood, Jr., who is Professor of Diseases of Metabolism at the Graduate School of Medicine, University of Pennsylvania. Next to him is Dr. Frederick W. Williams, who is Associate Clinical Professor of Medicine at the New York Medical College.

Without any further ado I would like to mention that we prefer this to be a rather informal colloquy, and we invite any of you to break in on any of the speakers. I shall present the first question to Dr. Duncan. Is it feasible, Dr. Duncan, or is it reasonably adequate therapy, in your opinion, to treat a diabetic without dietary regulation, and what is the place of the free-diet therapy in diabetes?

DR. DUNCAN: That question directed in New York City has quite a number of implications, seeing that free diet has the strongest proponents here, I suppose, of those favoring free diet in this country. My own feeling about it is, that the diabetes should be controlled—blood sugar kept as normal as one reasonably can and to do that the diet has to be *quantitatively* much the same from day to day—not the same foods but the same values. That can be achieved in the great majority of patients. It cannot be achieved in some patients with very labile diabetes. In these patients it is usually impossible to keep the diabetes under perfect control. When it is possible, I think it should be done. To allow them to eat a free diet, disregarding the amount of glycosuria or hyperglycemia, would appear to me to invite disaster sooner or later. It is a little like the man walking toward or along the edge of a cliff. My feeling is that you should be as far back from the cliff as possible because if the diabetes is not controlled

you are closer to trouble if an acute complication comes along. I think I might just finish up these remarks by saying that no patient will go into diabetic coma whose diabetes is controlled.

MODERATOR ANDERSON: Dr. Beardwood, how do you feel about this important matter?

DR. BEARDWOOD: Mr. Chairman, as Dr. Duncan has said, each time we near New York we are exposed to this sixty-four dollar question. Coming from a conservative city like Philadelphia, we feel, at least I feel, that in the management of diabetes, one should attempt, as one does in the control of other diseases, to approach the physiological balance which nature has provided and set up for those individuals who do not have diabetes.

I quite agree with Dr. Duncan, that I am never very happy when patients are not controlled and not on a definite program, and I think there is rather definite evidence that these patients are skirting the cliff and getting into danger.

It might be of interest, Mr. Chairman, that we have had before us the question of the employment of diabetics and the question of what standards one must accept, or at least what standards the American Diabetes Association would recommend, for such employment. In correspondence that we had with The Frigidaire Corporation, in Dayton, Ohio, which employs a fair number of diabetics, their experience with the so-called uncontrolled diabetic, the patient with high blood sugar and glycosuria, as far as injury and absenteeism was concerned, was so unfavorable that the company had set up the requirement that patients must have their diabetes controlled to continue work. They gave us figures on two comparative groups of cases and the time off from similar injuries and the amount of money collected in compensation, was, I think, some six or eight times greater in the group whose diabetes was not under what we at least consider control conditions.

MODERATOR ANDERSON: Thank you, Dr. Beardwood.

If there are further questions that the audience would like to submit, we should be very pleased to entertain and correlate them here and present them to our panel.

Dr. Allan, I see patients in the older age group who tend to run high blood sugar levels without showing glucose in the urine at all. How should these individuals be treated? Should an attempt be made to establish the textbook normals of blood sugar in these individuals?

DR. ALLAN: I feel, Dr. Anderson, that it is desirable to have the blood sugar restored to the normal level in these older patients with hyperglycemia providing one can accomplish that result without subjecting the patient to restrictions which become excessively burdensome. In these cases, I think one should aim to bring the blood sugar to normal, but should be satisfied with a slow move in that direction. A satisfactory diet with a dosage of insulin which will gradually reduce the high blood sugar level, is the best approach to the problem. I do not like to permit extreme hyperglycemia indefinitely.

MODERATOR ANDERSON: Dr. Williams, how do you feel about this matter?

DR. WILLIAMS: I think, first, that in the arteriosclerotic who has disseminated arteriosclerosis, and has a high blood sugar, we must be very careful about the speed with which we reduce it. I also think the length of time that it is down may affect the patient. I have definitely seen patients in this group or of this type who have all the signs of hypoglycemia yet have a blood sugar well within the limits of what we call normal. On the other hand, I want to call to the attention of every physician in this room the importance of a high blood sugar. In interpreting the finding of the blood sugar you should be aware of the time when it was taken. A single blood sugar observation, taken on a patient the morning of the day before yesterday does not give you much insight as to what the patient is doing right now, because we know that the blood sugar changes very rapidly. So I do not like to lay too much emphasis on the elevation of the blood sugar in an arteriosclerotic, for in the back of my mind I am not sure that I have not been instrumental in some pretty serious accidents in these arteriosclerotics by using insulin to bring their blood sugar down when the urine was sugar-free. Farfetched as it may seem and with no scientific support, with a blood sugar of 200 or 250 in an arteriosclerotic, I often question whether it is not a compensatory mechanism on the part of nature to assure the nourishment of the myocardium and the brain through the arteriosclerotic vessels.

DR. DUNCAN: Could I put in a word? Most of these patients about whom this question has been asked belong to the group that have "mild" diabetes, and we talked a great deal about the level of the blood sugar, probably justly so. I think the audience should realize that in most of these patients the control of the diabetes is relatively easy. With a small dose of the proper insulin, the proper selection of the diet and the proper

distribution used, control of the diabetes is usually an easy matter.

I would like to emphasize what Dr. Williams has said. He did not actually say that hypoglycemia predisposed to coronary occlusion, but it does. I saw in one hospital three patients at one time. Each of these patients had acquired a coronary occlusion during a hypoglycemic reaction. I would like to emphasize the ease of control of the diabetes in this group, but one must do it wisely and prevent at all costs a hypoglycemia.

MODERATOR ANDERSON: Dr. Duncan, these are considered the so-called "mild" diabetics, the so-called "touch of diabetes." I have often tried to emphasize the point that like a "touch of pregnancy," the touch of diabetes may have a very significant end result. Any diabetes at all is quite significant from the standpoint of vascular and retinopathic changes, and even though it seems to be a mild situation, it is something that should be taken care of adequately. You have emphasized that, I think.

DR. ALLAN: May I say a word, Dr. Anderson?

MODERATOR ANDERSON: Certainly.

DR. ALLAN: I think that one will usually find a tendency for the high blood sugar level to decline when there is continued absence of glycosuria. If the urine is really sugar-free all the time, one can hope for a trend for the better. On the other hand, if there is glycosuria of even a slight degree frequently or continuously, there is a tendency for continued elevation of the blood sugar.

DR. WILLIAMS: I would like to supplement what Dr. Allan said. The way to bring it down, rather than by the use of insulin, is by protracted dieting which is much safer.

MODERATOR ANDERSON: In other words, we return to our original point, that you cannot adequately control these individuals without dietary regulation of some sort. Diet is important, apparently, from what this panel has said on this point.

I should like to diverge at this point. Dr. Williams, what is your feeling about the use of hormones in the pregnant diabetic?

DR. WILLIAMS: I think nobody has had experience comparable to our friend Dr. Priscilla White, in Boston. Recently I have been able to treat one case with adequate dosage. Is that what you mean?

MODERATOR ANDERSON: That is right.

DR. WILLIAMS: I shall cite this one case. I know a single case proves

nothing, but this case, I think, will make those of us with open minds consider this method of treatment carefully. This was a young woman of twenty-six years, who had been a diabetic for fourteen or fifteen years, and was, according to Dr. White's classification, a poor risk (Class F). Her first pregnancy—before I saw her—ended in acidosis and abortion. Her second pregnancy was not attended with acidosis; she was carried along a little further. The first pregnancy terminated at about the third month, and the second one at about the sixth month by death of the fetus in utero—not acidosis this time. She became pregnant again, and was admitted to the hospital, when she had begun to develop signs of toxemia. The baby was alive at this time. While on a trip to Boston, I spoke to Dr. White about this case. She said that was just the type of case in which to use hormones. I asked her about dosage and where the hormones could be obtained. She very kindly arranged their procurement for us. The obstetrician, upon my return to the hospital, said, "We must interrupt the pregnancy of that patient. We don't want to lose the mother." We started the hormones and gave her, as I definitely remember, 125 mg. of both stilbestrol and progesterone intramuscularly, and within three or four days the obstetrician said he had never seen anyone get rid of edema, have the blood pressure and the amount of albumin in the urine drop as it did in our patient. We continued the hormones, and at intervals of two or three weeks we raised the dosage until she was receiving 250 mg. of each hormone daily. At the thirty-sixth week a cesarean section was done and a live baby obtained. I think that "one case" does not permit me to shrug off the hormone therapy.

MODERATOR ANDERSON: Dr. Beardwood, would you continue?

DR. BEARDWOOD: We have also been interested in this therapy. This is another sixty-four dollar question, each city having its own answer. I am glad to learn from Dr. Williams how he obtained this medication. I hope he got it for free. I understand it is pretty expensive. I have been impressed by the cases we have followed. We have not used hormones routinely in our cases. We feel that with proper control of the diabetes and watching the patient closely we have obtained fairly good results in our pregnant diabetics. I think the work that was done recently in Richmond was interesting. These patients were placed on this hormone regimen and then allowed to go into labor. The mortality in this group was comparable with that of any other group reported, whereas with careful control of the diabetes and in doing the section at eight and one-

half months, the figures were quite comparable with the figures of the group using hormones. I think the question is still open. I should be interested to hear what Dr. Allan and Dr. Duncan have to say about it, but we certainly do not use hormones routinely. We do use the hormones, probably to ease our conscience, if albuminuria occurs and hypertension develops, but our experience has been that the control of the diabetes and the careful management of these cases are equally important with section indicated at eight and one-half months. Apparently these youngsters get waterlogged from the eighth month on. That is the time you are apt to get in trouble from the standpoint of the fetus. Our experience has not been too bad even without the hormones.

MODERATOR ANDERSON: Dr. Allan, you have been rather close to the Deaconess Hospital—what is your impression on the use of hormones?

DR. ALLAN: I have been impressed by the data which Dr. Priscilla White has presented in regard to the beneficial results from hormone therapy in pregnant diabetics. We have followed her plan of treatment, where possible, but our own experience has been too limited to permit us to be certain of the source of benefit. I agree with Dr. Beardwood that careful attention to the control of the diabetes throughout pregnancy is certainly an important factor in insuring success.

MODERATOR ANDERSON: Thank you, Dr. Allan.

Dr. Duncan, how about you? This is an important subject.

DR. DUNCAN: I am not sure that the hormones help these women, but they make us feel better when the patient is given them. I believe this: The statistics, collected in Boston, are the best statistics available, and the burden of proof remains on the rest of us to show that we can do as well without them. We will have a difficult time doing that I am quite sure, but I think we must take into consideration that several things were done about the same time: First, they started doing cesarean sections earlier than previously. That would reduce the fetal mortality. Second, the increased protein, 2 grams per kilogram body weight, would tend to decrease the fetal mortality. The meticulous care that these patients have received at the Deaconess all adds up to a good result in the vast majority of cases, and I am not at all certain that that benefit should all be credited to the hormones. We give hormone therapy if Dr. Rakoff tells us on examination of the urine that it is needed, but I think that control of the diabetes is the important thing. Coming back to the first question, Mr. Chairman, I would say that the free diet in the pregnant

diabetic is a dangerous program. There the diabetes should really be controlled or the results will be poor.

DR. WILLIAMS: There is one more point I would like to add. For one who is about to undertake the hormone control or assay the reports of Dr. White and compare it with other reports, it is only fair to compare apples with apples. It is very important that all of the cases be classified under the criteria that Dr. White has offered in classification: Duration of the disease, duration on insulin, previous history of bad results in pregnancy, and evidence of arteriosclerosis. Let no one abandon hormones unless he has used what Dr. White considers adequate dosage. I have had a few cases in which I had previously tried hormones, and Dr. White joshed me about my doses being homeopathic.

MODERATOR ANDERSON: I see here a question related to this subject: How carefully should glycosuria be controlled in the pregnant diabetic? I see there is a catch in that. Dr. Duncan, will you discuss this?

DR. DUNCAN: It is very difficult to control the glycosuria in a pregnant diabetic because these people have a reduction in the renal threshold, and while it may be of some help to examine the urine for the amount of sugar that is lost, because they do lose sugar when the blood sugar is not high, about 130-140 mgm. per cent, this decrease in the renal threshold disappears after the pregnancy is over. The same is true in the thyrotoxic patient, and so one has to rely more on the well-planned taking of blood for analysis—I don't mean just the fasting specimen, but if things are going along fairly well, a curve of the day's blood sugar before each meal and at bed time, if that is practical. That will give us a great deal more information as to how to guide our insulin dosage for these patients. These patients have an emergency existing for nine months; so these special curves, though they require quite a number of tests, are very important, I believe. After all, a life is at stake.

MODERATOR ANDERSON: I would like to change to another subject at this point. Dr. Beardwood, have you any suggestions for the treatment of diabetic neuropathy? That seems to be as troublesome in this part of the country as elsewhere.

DR. BEARDWOOD: We have ideas about diabetic neuropathy. Certainly, a well established diabetic neuropathy is one of the most distressing complications of this disease, and Dr. Yaskin and I—Dr. Yaskin is Professor of Neurology at the Graduate School—have been interested in this for some years. Dr. Yaskin is sure that the best treatment for neuropathic

diabetes is six months. It takes almost that long for all these symptoms to disappear. We believe that the results are obtained—again this seems to be the theme of the meeting—by controlling the diabetes and by the use of relatively large doses of B_{12} daily—probably 60 to 90 micrograms parenterally, and by physiotherapy. I think that in the vast majority of cases of diabetic neuritis that we have seen, we have thereby been able to get them over the acute stage, the acute discomfort, and progress from then on has been relatively slow. We have not had an opportunity to use the newer pregnant mare's liver, the name of which I have forgotten, in a great many cases. Dr. Collens and Dr. Rabinowich used it in their cases. Dr. Rabinowich's results in two were good, and the results in the other two were not as encouraging. However, no one can draw conclusions from a small group of cases. I think it is very important also to remember that a fair number of cases of diabetic neuritis are associated with marked and advanced peripheral vascular disease, and possibly in some cases, attempts to manage that condition will be of some value.

We have recently been using a pancreatic extract preparation which is quite different from the one that had been used before, and here again, in some cases, we have obtained fairly good results. Diabetic neuritis certainly is a difficult condition to treat if it is well established with pain and absent reflexes and the other common symptoms. Fortunately we have seen but few cases of so-called diabetic tabes, they being the most difficult of this group to handle. I think it is worth while to have physiotherapeutic aid, to give large doses of B_{12} and possibly this new pregnant mare's liver preparation that Dr. Collens developed.

DR. DUNCAN: Hepulin.

DR. BEARDWOOD: I think Dr. Duncan has used hepulin more than I have.

DR. DUNCAN: No, it is too expensive.

MODERATOR ANDERSON: I see you all have the same difficulty that we have. We all go through the same throes in therapy of the neuropathies. Dr. Allan, what has been the experience of your group?

DR. ALLAN: Dr. Anderson, we cannot boast of any good therapy for diabetic neuritis except for long continued, good control of the diabetes; it is important to emphasize the *prevention* of diabetic neuropathy. Diabetic neuropathy tends to appear in the neglected cases of diabetes, not necessarily the bad cases—the patients in danger of losing life—but those in which the diabetes is so mild that it does not seem to

demand any attention.

As an example, I might tell about a man I saw yesterday, a physician, who has suffered greatly from pains of neuritis since last January. These pains are beginning to disappear now but through the greater part of this year he has endured agony in spite of all the remedies which he has tried. This doctor found that he had sugar in the urine in 1941. He tested his urine before he enlisted. He found sugar and cut down on his food consumption. He had been a hearty eater. A short time afterwards he found that his urine was sugar-free, and he went for his examination. He never considered himself to be a diabetic, and he never had tested his urine again until last March. He was humiliated to think that he had let this condition creep up on him as it did. During all of these years he had presumably had diabetes of minimal degree. Now in this year 1952 he has suffered the consequences of neglect. If there had been just a little regulation of the diet, he might have escaped the trouble which has affected him so seriously and painfully.

MODERATOR ANDERSON: Mention has been made of homeopathic doses. I wonder whether any of the panel have had experience with large doses of B_{12} such as 1,000 micrograms a day, a milligram, and what the experience has been with that, Dr. Duncan.

DR. DUNCAN: I have had two patients who had nocturnal cephalgia and the dose of as much as 100 micrograms daily intramuscularly had no effect. When given 500 and later 1000 micrograms daily, there was a prompt improvement in each of these two patients. I don't think that proves much, but I have become very much attached, as I think Dr. Beardwood has, to the effect of vitamin B_{12}. I mention that because the group at the Deaconess, for whom I have the greatest respect and friendship, don't believe that one gets much benefit from vitamin B_{12}. Recently on a panel at Cleveland, Dr. Marble said he believed the benefit we got was from the control of the diabetes. I plug for the control of diabetes all right, but it is very important to realize that many of these patients with chronic neuropathy, with the burning feet or numbness, notice a very definite improvement after the first or second dose of vitamin B_{12}. That has nothing to do, I believe, with the control of the diabetes, which may take several weeks.

One other point, and I am through with this: In these patients with acute neuritis, such as sciatica, when you get a virgin diabetic with neuritis of this type, in my experience, he often becomes worse in the early

stages of the control of the diabetes, particularly in the obese patient, whom I generally put on a reducing diet. Perhaps that has something to do with it. I warn either the patient or a relative that this patient may get worse during the preliminary treatment for this very painful complication of diabetes.

MODERATOR ANDERSON: I think we have all noticed that, and have been rather discouraged with this development,—because just when we wanted to keep the patient in a suitable frame of mind to follow our dietary regimen, he has balked because he seemed to be getting worse. We have had the same experience as you with the larger doses of B_{12}, and I think it merits further trial in diabetes.

I might mention another point. It is so convenient and easy for the patient to administer B_{12} parenterally to himself with the same syringe he uses for the insulin but, of course, at a different time. It is given with much more facility than is liver extract.

Have any of the others had any experience with hepulin?

DR. DUNCAN: As I have said, we have used it in a few patients. One patient that I know, I believe, got results; two patients quite indifferent results. I think in all fairness to the product we did not continue as long as we should have to give it a fair trial.

One other point about impotence. I think it should be looked upon as a diabetic neuropathy. I have seen several patients who have had impotence corrected. I had not seen that occur to the same degree from any other treatment that I had observed before.

VOICE: Is a question in order?

MODERATOR ANDERSON: Yes, please.

QUESTION: My name is Dr. Salzman, and I double in brass. I double in brass because, first of all, I treat diabetics and, secondly, I *am* a diabetic. That adds more interest to the situation. May we ask Dr. Beardwood to go into more detail on his treatment of the neuropathy as associated with peripheral vascular diseases? He has said that he uses B_{12} in heavy dosage, controls the diet, gives physiotherapy and a pancreatic extract. Is that pancreatic extract the same as Depropanex put out by Sharp & Dohme or is it the pancreatic extract which your fellow Philadelphian, Joseph Wolf, is using? What is the type of the pancreatic extract?

DR. BEARDWOOD: It is yet another type of pancreatic extract which supposedly has in it a vasodilating effect. It is not the same preparation

Dr. Wolf used. It is not Depropanex. It is not available on the market as yet, and I am not sure that there has been enough work done on it to justify its release. I am not familiar with the actual technique of its extraction, but it is supposed to do two things: to produce a vasodilation, and to deplete the cholesterol or diminish the cholesterol content of the vessel wall. It has the ability certainly, to decholesterolize the livers of experimental animals. One is dealing with a slightly different condition in the atherosclerosis of the diabetic. This drug is supposed to have these two functions. I don't believe it has a name yet, but it is different from the other two.

DR SALZMAN: That sounds like the work of Wolf with Polyponcaine at Valley Forge.

DR. BEARDWOOD: It is an advance. I know something about Wolf's work. This is a preparation which is a bit like the one he is using but supposedly more potent. Does that answer your question?

DR SALZMAN: Thank you, it does.

MODERATOR ANDERSON: Any further questions from the floor while we are at it?

QUESTION: What damage, if any, does repeated insulin shock do to the brain tissue of the young diabetic child?

MODERATOR ANDERSON: Dr. Williams would you like to answer that?

DR. WILLIAMS: I think the damage to a young central nervous system suffering from hypoglycemia can be, in fact I know it can be, very permanent. I have one outstanding case in my own experience of a diabetic child who was brought into the hospital in acidosis. The attending physician ordered some insulin. The child was unconscious and over the telephone more insulin was ordered, and the youngster remained in insulin shock for 24 hours. This youngster, now at the age of five or six, is living with a hemiplegia, so that the damage may be permanent. I think the damage to the child's brain results from two things: One, the duration of the insulin shock and two, the frequency of shocks. I think the adult nervous system can resist the protracted shock better than the youngster's. On the other hand, I think the child can be permanently affected. We have seen some of these at the camp for diabetic children. They have had a difficult diabetic management over a period of years with many repeated shocks. These children seem to exhibit a retarded mentality. They are a little below the average in all ways. I don't know enough about neuropathology to tell you what has happened.

MODERATOR ANDERSON: Dr. Duncan, have you any thoughts on that?

DR. DUNCAN: No, except that I have seen one patient in particular following the termination of a successful pregnancy who had a profound hypoglycemia, and she has not had complete restoration of her memory since. Maybe it is just as well. She does very well. She enjoys a very happy family life, but the fact remains that there was some change in her ability to remember things since that hypoglycemia.

MODERATOR ANDERSON: That came during pregnancy or following pregnancy?

DR. DUNCAN: Following pregnancy.

MODERATOR ANDERSON: It reminds me of Dr. Williams' pet subject, pituitary necrosis. One of the outstanding points is hypoglycemia, is it not, Dr. Williams?

DR. WILLIAMS: I am the "one-case" specialist. This was an interesting girl, a known diabetic, and her diabetes was unstable at first. She gave no history of endocrine disturbance during adolescence. At maturity her diabetes was fairly well managed for a few years, and then she married. In the third month of her pregnancy I was called to her home. She was in a hypoglycemia, and some orange juice promptly brought her out. I reduced the insulin for the next day, and the following day she was all right. But on the day after that I was called again, and this time I needed intravenous glucose to revive her. We reduced the insulin from her usual dose, which I think, was 60 units, down to 10 units. The next day she was in shock all day; evidently this occurred when she was at the breakfast table, for she was found at the same breakfast meal at four o'clock in the afternoon. We then took her into the hospital, but she never did come out of the hypoglycemia despite intravenous administration. We restored the blood sugar to normal and succeeded in raising her spinal fluid sugar to normal. Then she again showed four plus urinary sugar and a trace of acetone. We gave her a dose of 10 units of insulin with an infusion and she at once had another reaction. We gave her intravenous glucose again, but she died. The postmortem showed nothing except an acute necrosis of the pituitary gland. Evidently this was the counterpart of a Houssay animal in a human being, and occurring during pregnancy. Pituitary necrosis has been reported before, but occurs rarely during pregnancy. Dr. Allan, I am sure, will say something about this. We reported this in "*Diabetes*," the *Journal of the American Diabetes Association.*

MODERATOR ANDERSON: Will you elaborate on this Sheehan syndrome?

DR. ALLAN: The change in the character of diabetes with the development of pituitary insufficiency is very important because it may give us more insight into the nature of diabetes itself and its complications. There now have been, to my knowledge, about eight cases in which there has been an amelioration of diabetes with pituitary damage. One case of particular interest was reported at the meeting of the International Diabetes Congress last July. This was a case seen by Poulsen* in Denmark in which severe diabetes became very mild after pregnancy. There were clinical features which showed pituitary insufficiency but the condition was not fatal. It was found that the diabetic retinopathy which had previously been present had subsided to a very large degree. This would suggest that the development of this complication in diabetes is connected with activity of the pituitary. It makes one think of the possibility that if the pituitary action could be regulated or diminished in a suitable manner without producing ill effects, there might be benefit in regard to diabetic retinopathy and perhaps other sequelae of uncontrolled diabetes.

MODERATOR ANDERSON: I suppose this case of yours was before ACTH had become so prominent, Dr. Williams. You probably would have used that. I think some cases have been reported since then in which it has been used.

DR. WILLIAMS: It was before steroid popularity or it surely was not available then, but I don't think it would have helped us because there were two things to be considered clinically. Here was a girl in severe hypoglycemia from breakfast until 4:30 P.M. The inference is a protracted hypoglycemia, and one might expect some irreversible brain damage. At that time the diagnosis was not pituitary. After getting her to the hospital, we discovered her sensitivity to a small dose of insulin. When we had corrected her hypoglycemia and were still unable to revive her, the appearance of acetone led us to suspect that the condition was pituitary in origin.

DR. BEARDWOOD: May I say a word, please?

MODERATOR ANDERSON: Yes.

DR. BEARDWOOD: I think these cases of pituitary insufficiency are very interesting. However, there is probably a much more common endo-

* Poulsen, J. E. Houssay phenomenon in man; recovery from retinopathy in a case of diabetes with Simmonds' disease, *Diabetes* 2:7-12, 1953.

crinopathy which will result in a rather sudden decrease in the insulin requirements, namely, Addison's disease. There have been reported in the literature quite a few cases, far more cases of Addison's disease developing in the diabetic than pituitary cachexia. We have had two such cases, and we frankly were puzzled for a while as to why it happened. In the first case, a patient who had been taking 50 units of insulin for some years and who over a period of six weeks required but 5 units, was found to be bordering on a crisis when he arrived at the hospital. I think it is important to remember that this can occur, and it can occur in a diabetic of some years' standing. Of the two cases that we have seen recently, one had had his diabetes twenty years and the other patient had had hers for five years, so that any definite diminution in the insulin requirement should arouse some suspicion of the adrenal in the pituitary-adrenal axis.

I should like to say one more thing. I think it is unusual that permanent central nervous system changes in children are common. I don't think Dr. Williams and Dr. Duncan have found that they are. We must be careful in using insulin in the diabetic child. The permanent damage to the central nervous system is rather the exception than the rule These kids stand hypoglycemia well, and this thought should be injected.

DR. WILLIAMS: Yes—it is not the common and frequent observation; it is the unusual.

MODERATOR ANDERSON: Dr. Duncan, do you have any suggestion for the prevention of insulin atrophy?

DR. DUNCAN: You mean at the site of injection?

MODERATOR ANDERSON: Yes.

DR. DUNCAN: I am being needled, I can see. Yes, I have. The answer is I have had several patients with fat atrophy with indentations of the skin. I have seen several patients in whom the only change made in the program was to tell them not to refrigerate the insulin that they were currently using. That does not correct all of them. We know that. We know that the drug addict gets the same sort of fat atrophy and indentations but I believe that 50 per cent in the diabetic are due to using cold insulin.

DR. WILLIAMS: I would like to put a word in about refrigeration as a duty of the editor of the Forecast Magazine, the magazine for diabetics which the American Diabetes Association puts out for the patient. The

question of refrigeration of insulin presented quite a problem to the editor who wished to publish an article for the patients of the country that would satisfy both the pharmaceutical manufacturers and the practitioners treating these patients. Different viewpoints were expressed and I can bring this conclusion to the meeting: It is not necessary to refrigerate a bottle of insulin which the patient is currently using. There are only 400 or 800 units in the bottle. If the patient uses 40 units a day, or anywhere from 20 to 40 units, he will use up that bottle in 20 days. Unless he places the bottle in a very warm spot in the house or in direct sunlight, there will be very little change. The reason the wrappers indicate that insulin must be kept cold, is to get maximum effect unit for unit up to the expiration date on the wrapper. Accordingly, insulin must be kept cold in transportation, in storage by the dealer, the middleman and the local retailer, and even by the patient who buys enough for three or four months at a time, or if he buys ten bottles at one time, nine should be put in the refrigerator and the bottle in use left out. I think that we should all agree that such routine does not cause deterioration of the insulin. There may be some minimal loss of insulin, but not enough to be of any practical importance. The units of insulin are not in tenths of units.

DR. BEARDWOOD: May I ask Dr. Duncan if there is a factor other than chilling, because practically all patients take insulin at about the same temperature? We have seen more of atrophy at periods of what you might call metabolic unrest—puberty, in the growing period of youngsters, in the adult with hyperthyroidism. I must admit that our patients who get insulin atrophy and those who do not, use the same refrigeration methods. I wonder if there is not some other factor that is active.

DR. DUNCAN: I think there must be some other factor to explain the occurrence of this disorder when they are using room-temperature insulin, and we also have noticed it. It is more common in young girls and in females in general than it is in males. As a matter of fact, it is rather uncommon in my experience in the male patient, so that there are other factors.

MODERATOR ANDERSON: Dr. Beardwood, I would like to introduce another subject. The request is: Kindly outline the principles of therapy in diabetic retinopathy. That has been one of your pets. I would like you to start the ball rolling on that.

DR. BEARDWOOD: Mr. Chairman, I will be glad to. As we see it, the management of diabetic retinitis, concerning which there is a great deal of confusion as to etiology, can be divided into two definite steps: First, prophylaxis. We feel—and here again we get back to what seems to be the main topic of today—that the balanced diabetic has much less tendency to develop diabetic retinitis. We will soon have some figures to present which I think will show that. Now the literature on the incidence of diabetic retinitis is a literature which has been reported mostly by the eye men who see diabetics treated by a variety of clinicians and probably by a variety of standards; so that, as Wagener has reported, 10 per cent of diabetics of five years' duration have retinitis—I don't think that this figure necessarily holds for all diabetics. I am sure it does not hold in the series we have checked over for retinopathy—in other words, the eye people see the diabetics that have eye trouble to begin with. We feel very definitely that control of diabetes is a very important prophylactic factor.

Another factor we have been interested in—and every time I come to New York I get "the needle put into me"—is the use of rutin. We have felt in those cases with an increased capillary fragility that have retinitis, rutin or any capillary drug given in adequate amounts to control the fragility has definitely helped in the prevention of fresh hemorrhages. We are now running a series of cases, juvenile diabetics, who have increased capillary fragility, no retinitis, no Kimmelstiel-Wilson disease as yet. We only started a year or two ago, so one does not know what will happen in ten or fifteen years. Retinitis is so often associated, as you know, with the picture of Kimmelstiel-Wilson disease, or diabetic nephrosis, or whatever you want to call it. Certainly in the group of cases that we saw they all had a very markedly increased capillary fragility.

The third thing, this diabetic nephritis, be it Kimmelstiel-Wilson disease or the result of chronic pyelonephritis with chronic infection, is often difficult to disentangle. Clinically, the two conditions may coexist. We feel here again from a prophylactic standpoint, clearing up of urinary tract infections, particularly in the female, and keeping them cleared up, is a very important factor in the prevention of future trouble. Once diabetic retinitis has occurred, we feel that control of the disease is important. There are two schools of thought; Dr. Tolstoi, Dr. Dolger, Dr. John Fell, and Dr. Friedenwald in his recent

paper, feel that the control of the diabetes once the retinitis has occurred is of no particular moment. However, there are just as many papers from the other school which seem to show, and we feel so too, that the control of the diabetes even after the retinitis has developed is helpful unless one has a fulminating type of Kimmelstiel-Wilson disease, in which case it does not make much difference what you do.

We have used rutin in those cases in which the retinitis has occurred and which have had increased capillary fragility, in an attempt to restore increased fragility to normal.

Dr. Truman and I have also been interested in roentgen therapy in diabetic retinitis particularly retinitis proliferans, and we reported a series of cases at the American Diabetes Association meeting last summer. We x-rayed approximately fifty-seven eyes which had advanced retinopathy with retinitis proliferans. We obtained improvement in about 33 per cent, the improvement being in two respects: First, a better visual acuity on the patient's part, and second, changes demonstrable to the ophthalmologist that the proliferating retinitis had been burned out or had subsided. We obtained fair results in about 23 per cent of our cases, so that in over half the cases we treated—and they were cases that were selected because they were pretty well advanced and were bordering on blindness—we believe we have obtained sufficiently good results to warrant continuing this treatment.

The technique must be carefully carried out,—the posterior segment of the eye alone exposed. This treatment does nothing to retinal hemorrhages. That is another story. Although when one has a retinitis proliferans which occurs late in diabetic retinitis, this treatment is of value.

MODERATOR ANDERSON: I think you mean by being "careful" to shield the rest of the lens. Have you encountered any cataracts as the result of this treatment?

DR. BEARDWOOD: We followed some of these cases for over two years, and we have not found any evidence that cataracts have developed. When we began, several of these patients had certain changes in their lenses, and they progressed about as one would expect in a year and a half or two years' time. We have been fortunate so far in that we feel we have not produced roentgen cataracts.

MODERATER ANDERSON: What dosage of rutin do you usually use?

DR. BEARDWOOD: We usually use 150 mg. a day and push up to 300 mg. a day if we don't note some improvement in the capillary fragility.

MODERATOR ANDERSON: Dr. Williams has recently presented a fourth principle in the treatment of diabetes: The first, diet; second, insulin; the third, exercise; and he has a fourth which should be emphasized by him as the Editor of the Forecast.

DR. WILLIAMS: Evidently we are now up to the "commercial." The American Diabetes Association produces a magazine for the patient which is published six times a year. It is called the American Diabetes Association "Forecast," and subscriptions can be had from 11 West 42nd Street. This magazine contains authoritative articles by experts. It also contains articles by outstanding diabetics who have been able to accomplish things, like Swish Nicholason the outfielder for the Philadelphia National League team, Billie Talbert, Ham Richardson, Clair Ryder, and the rest of the diabetics who, we know, have been able to master their disease well enough to go on and be leaders in the community. In addition to that, "Forecast" contains the Children's Department, a Recipe Department, a Question and Answer Box, and a little column called Dave's Diary, which is the diary of a diabetic. In this way we are trying to supplement the treatment by the doctor. The magazine is intended to be a supplement to and not a substitute for treatment. The basic A-B-C's on how to test urine, what diet the patient should be on, how much insulin, and everything else, *are in the doctor's hands.* This is an attempt to help the diabetic to make a philosophic adjustment to his disease and enable him to be a useful and active member of the community.

MODERATOR ANDERSON: Ladies and Gentlemen, have you any further questions that you would like to present to the panel at this time?

QUESTION: Did I understand correctly that you don't lay too much stress on the blood sugar in the elderly diabetic or in the elderly patient without glycosuria? How do you approach him then in the preoperative phase or when he has any ulcerations of his extremities?

DR. BEARDWOOD: I think the impression was wrong that we are not concerned with the blood sugar levels. In Philadelphia we probably depend more on the blood sugars than we do on urines in studying the patient. We would handle an elderly diabetic the same as a young diabetic. Before surgery, we would want the blood sugar to be at a satisfactory level, if possible. Such a level as far as I am concerned for a patient of 65 or 70 years would be 150, 160, 180, or 190 preoperatively. I don't care what the blood sugar is so long as it is somewhere within

reason preoperatively, because you can adjust it postoperatively. We have seen many patients who have been too well controlled before surgery, particularly surgery which was done for infections, and when the infection was relieved, the insulin requirement suddenly was lessened. Those patients who have been sent to the operating room with a blood sugar of 60 or 70 have gotten into trouble. From the same standpoint of low blood sugar, many elderly diabetics have a certain amount of coronary insufficiency. There again, I think, as Dr. Allan and Dr. Williams brought out, it is rather important that we let their blood sugar ride a little higher than the accepted normal limit. We would be happy with a blood sugar of 140 and 150.

MODERATOR ANDERSON: That clarifies the issue. The panel is not disregarding high blood sugar.

DR. WILLIAMS: I would like to point out something in this regard because I am particularly interested in the surgery of diabetics. I believe that preparation of a diabetic for surgery cannot be based on a single blood sugar determination. I am quite sure that every doctor here realizes that a patient with a blood sugar of 110 who is dehydrated and who has been depleted of protein and has been starved for the preceding six weeks, would not be a good risk just because a single blood observation happened to fall between two numbers that were once designated as the limits of normal. It is very important that a preoperative diabetic patient must not have acidosis. He must not be dehydrated. He must not be depleted of electrolytes. He must have had adequate protein nourishment previous to elective surgery as well as adequate carbohydrate utilization. For at least two or three days before he is operated upon he should be in protein anabolism. Except in acute conditions where urgent surgery is indicated, this should be observed. Accordingly, the patient must have been on an adequate diet, adequate in protein, minerals, fluid, electrolytes and carbohydrate. He must have utilized sufficient carbohydrate to spare his endogenous protein so that he is in positive protein balance. He must have received enough protein in his diet to provide him with an adequate supply of amino acids. If your diabetic patient is in protein anabolism, his hyperglycemia and glycosuria sufficiently controlled, whether he needs insulin or not, is more important than whether a single blood sugar on the morning of operation was 100 or 190. I believe this is a very important point: Every diabetic's blood sugar can be brought within normal range. Any doctor can get it normal

within a very short time with the use of regular insulin, and the patient may still not be a good operative risk.

MODERATOR ANDERSON: I think the entire panel would subscribe to that philosophy. I don't think there could be any possible disagreement with that. In that same connection on diet, in the "opathies," retinopathy and neuropathy, the matter of protein has been emphasized also from an anabolic aspect. Are there further questions?

QUESTION: Is diabetic control or the lack of it related directly to Kimmelstiel-Wilson disease or renal complications in diabetics?

MODERATOR ANDERSON: Dr. Duncan.

DR. DUNCAN: I believe that it occurs more frequently in individuals whose diabetes has not been well controlled, but it may occur in very mild diabetes; as a matter of fact, it may occur in an individual before the diabetes is manifest, which would make you think that the control of the diabetes did not play much part, but I believe it does. There are certain things that occur in the pre-diabetic state that are very much the same as when they become prominent after the diabetes is manifest.

Another example of this is the big baby born of the pre-diabetic mother, the baby weighing 10 lbs. or more, and yet the mother has not diabetes, but in five or ten years she develops it. I have seen several patients now who have had Kimmelstiel-Wilson syndrome in the milder stages, and certainly the diabetes can occur in Kimmelstiel-Wilson disease in very mild form, but I think it is a mistake to believe that it only occurs in the mild diabetic as has been claimed by some, because we know that it occurs in severe diabetics as well as in the mild.

MODERATOR ANDERSON: Thank you, Dr. Duncan.

DR. WILLIAMS: I would like to ask Dr. Garfield Duncan what is "mild diabetes"?

DR. DUNCAN: That is very simple. Mild diabetes is a diabetes that can be controlled without insulin. That is mild diabetes. It may have acute exacerbations, with blood sugars going very high. I had a patient with an acute pyelonephritis; he did not require insulin before he got this infection but during infection he required over 800 units of insulin a day. Subsequent to the clearing up of infection, he did not require insulin. He had an inherent mild diabetes. If you can control the diabetes without insulin and have the patient's nutrition properly looked after, the aim being that his weight should be ideal, that I call a "mild"

diabetic.

DR. WILLIAMS: I am glad to have your definition because I am interested in some sort of nomenclature, if we are going to classify diabetes as either mild, moderate or severe. I think there is much confusion in this because many people say, "Oh, this patient is a severe diabetic. He needs 50 units," and this patient on 50 units balances his diet and insulin well enough and he rarely if ever gets any of the complications for fifteen or twenty years, but the one you call mild, that is readily controlled by diet sans insulin, comes down with all the vascular complications and he very frequently comes to an early end. I wonder then was his diabetes really "mild." I don't like "mild," or "moderate."

MODERATOR ANDERSON: I think that is really brought out to an extent by the so-called "cold." We all know what you mean by a cold, yet it is rather hard to define. I think the danger of the "mild" classification is that the patients may get the impression that since their disease is mild they do not need to bother about it. I, personally, would like to see a complete professional disavowal of the term "mild diabetes." It is or it isn't diabetes, even though we have to put one plus, two plus, three plus, four plus for our own clinical classification of degree of severity.

DR. DUNCAN: I don't think we need do any such thing, I don't agree with Dr. Williams. I believe that in these other mild diabetics that come to an early end, it may not be related to the diabetes at all. We know the obese diabetic is a notoriously mild diabetic. We know that because it is so readily controlled by a reduction in weight. We also know that even if he did not have diabetes he would die a lot earlier than an individual with a normal weight. I would like to say that there is a tendency to classify the grade of severity of diabetes by the amount of insulin used. That, of course, is very erroneous because the very fat diabetic is relatively resistant to insulin and might take 150 units of insulin a day to control his diabetes, yet we know you can control that diabetes by reducing his weight 10 or 15 lbs. I should think we certainly could classify them into two groups anyway, and in that way Dr. Williams and I could get together. I would put as one, the patient who would be on the mild side if you can control his diabetes and maintain good nutrition without insulin in the absence of complications, and two, as the more severe type, the one who must have insulin to maintain control of the diabetes and maintain good nutrition.

MODERATOR ANDERSON: Doctor, you had a question?

QUESTION: Every now and then we encounter some difficulty with the newborn baby of the diabetic mother. We investigate and find some bizarre manifestations like water-logging and a large liver. Blood is taken, and one finds that it resembles that of the erythroblastotic infant. What is your view of the abnormal physiology which is responsible for that?

MODERATOR ANDERSON: Dr. Allan, would you like to answer that?

DR. ALLAN: I should like to pass the question to Dr. Duncan. He looks as if he knows the answer. I don't.

DR. DUNCAN: I don't know but I suppose it is on a hormonal basis. We have as much trouble in Philadelphia as they have in Boston. These babies seem to blow up with fluid. I am not sure what Dr. Allan's patients have had but the babies of the diabetics that I have seen, if the diabetes is well controlled, have not been as large as those reported in the literature, and have not had as much trouble as Priscilla White writes about, edema and swelling of the face and of the body in general. Just in the past week we lost the first baby of this type in quite a number of years. I want every baby born of a diabetic mother to be fed every two hours for three days from the time it is born. This baby was in another hospital and the pediatrician did not agree with this plan, and the baby died. At autopsy the baby had atelectasis, a common cause of fatality in these babies, but why do you suppose the baby had atelectasis? I raise the question, did the fact that this patient had hypoglycemia have anything to do with the atelectasis? In view of our good results when we feed the baby every two hours for the first three days, I am inclined to believe we have overcome some of these difficulties. Priscilla White does not follow this regimen, yet she has excellent statistics.

MODERATOR ANDERSON: One more question.

QUESTION: May I ask a question that may seem a bit foolish? The purpose is to get an expression of opinion from your panel on the timing of insulin. The reason I ask is this: We have been taught since the longer-acting insulin has been in use (I particularly refer to the protamine zinc insulin) that it should be given at seven or eight o'clock in the morning. It seems to be a rule without much foundation. Yet there are many individuals who take only a very light breakfast, a very light lunch, and have their largest meal at six or seven o'clock in the evening. Is there any special reason why that insulin should not be given, let us say, at

eleven or twelve o'clock in the morning rather than seven?

MODERATOR ANDERSON: Dr. Beardwood, would you like to take that on?

DR. BEARDWOOD: As I understand the question, is it protamine insulin alone that you are speaking of?

QUESTIONER: Correct, sir.

DR. BEARDWOOD: Well, of course, if protamine zinc insulin works as it ideally should, one would probably get a level blood sugar throughout the twenty-four hours. There is probably no reason why protamine zinc insulin could not be taken at eleven or twelve o'clock in the morning if that was the schedule the individual was on. Our philosophy in the treatment of diabetes has been to make it as easy as possible. Most people are home in the morning for breakfast and take the insulin and the rest of the day are unburdened. I remember a few years ago, if I may report a case, Mr. Moderator, we were experimenting with a regimen of a 36-hour-acting insulin. We had a farmer diabetic in the hospital. He did very well with this insulin. We then decided to give it at ten o'clock in the morning. He had to farm and sell potatoes or whatever they do at this time of day. Our great scientific research on this fellow fell flat because he would not take insulin at ten o'clock. He took a mixture at another time and did all right on that. By and large, we have to consider the insulin dosage in long acting insulin in relation to the patient's convenience. I certainly think that with the other insulins, NPH and globin insulin, there is a very definite reason for taking them early in the day. I think you could well in your individual case give the protamine zinc insulin around noon.

One more case, if I may, very embarrassing. One of my youngsters went to the diabetic camp, and the doctor called me up and said, "Why do you give this patient protamine insulin at night?" He had been taking it at night unbeknown to me and had been doing very well. Each time he came in I would readjust the insulin. I did not know he was taking it at night.

MODERATOR ANDERSON: Ladies and Gentlemen, regrettably our time is up, and I want to take this opportunity to express for the Academy our gratitude to the members of this panel, and, I am sure, your own attention to their answers bespeaks your interest in their discussion.

EXFOLIATIVE CYTOLOGY AS A SCREEN TEST FOR URINARY TRACT MALIGNANCY*

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THE study of stained exfoliative cells in urinary sediment first received its impetus from the work of Papanicolaou.[1] Abnormalities of cell structure and appearance subsequently led other investigators, Ludden and McDonald,[2] Daut and McDonald,[3] Schmidlapp and Marshall[4] and others to extend its application. Their conclusions bore out the value of such a diagnostic procedure and indicated that this might serve as a useful screen test for the detection of carcinoma of the urinary tract. The ease of collecting specimens, the low cost, and the rapidity with which the examination could be performed, suggested the advantage of such an investigation, should it prove reliable. No attempt has been made to replace the usual urologic armamentarium of cystoscopy, pyelography, biopsy, or perirenal and retrosacral air insufflation, but only to add an adjuvant diagnostic aid for the detection of unsuspected malignancy. That this is possible was proven by Papanicolaou and Foot[5] in the case they diagnosed as renal carcinoma which was found only after serial sections were examined.

Material was obtained from the clinics and wards of the University Hospital, Bellevue Hospital, 4th Division Urology, and private services of the physicians on the staffs of both institutions. Specimens from both male and female patients were taken at the time of the initial examination, voided in the former, and catheterized in the latter. In addition, ureteral specimens were examined, in indicated cases, from both renal pelves, so that comparison might be made. This was done not only to localize the site of the tumor, but also to avoid the error of a false positive diagnosis. Bunge and Kraushaar[6] demonstrated the similarity of cancer cells to those of normal metaplasia of the renal pelvis epithelium. To the specimen of urine was added an equivalent amount of 95 per cent

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alcohol. This was delivered to the laboratory within three hours, thus insuring fresh samples with little or no changes in the exfoliated cells, and with all the material available for smears. The only restriction imposed was that all specimens from men were to be from patients who had no urethral discharge, so that the exfoliated cells would not be contaminated by large numbers of inflammatory cells. The smears were then stained by the method of Papanicolaou.[1]

Patients from whom samples were taken were unknown to the investigator, as to symptomatology, reasons for seeking medical attention, or previous diagnosis. The only information sent with a specimen was the name and age of the patient. Examination of the urine was the first laboratory diagnostic procedure done, obviating any possibility of clinical suggestions influencing the examiner. Cases included all types of urologic disease which might occur in active urologic practice. Smears were reported as negative, suspicious, and positive. A report of "suspicious" was an indication for further study, and additional specimens were requested. In the compilation of the statistics, the classification of suspicious was not included, as all such, on repeated examinations, proved to be either positive or negative. A clinical diagnosis was eventually made in all, either by surgery, biopsy or definite clinical study. All cases reported as positive were confirmed by surgery.

In order for this procedure to be employed adequately as a screening test for urinary malignancy, all types of urologic disease were included, with the exception of urethritis. Thus, vesical calculus secondary to a contracted bladder neck of inflammatory origin would not require either a surgical specimen or a biopsy to rule out a malignancy of the urothelium.

A total of 596 slides from 500 different patients was examined. Slides with insufficient material were not considered and repeat slides were obtained until sufficient material was seen. Among the 500 patients were six cases of carcinoma of the prostate. At the University Hospital, little success has been obtained with voided specimens in the diagnosis of prostatic malignancy, corroborating the work of Chute and Williams.[7] At present, the technique for collecting material for this condition is to massage the prostate on a full bladder, collect the voided specimen, spin down the sediment, and then stain and examine. As this report is concerned primarily with malignancy of the urinary organs, the six cases of prostatic cancer were discarded, reducing the total number to 494.

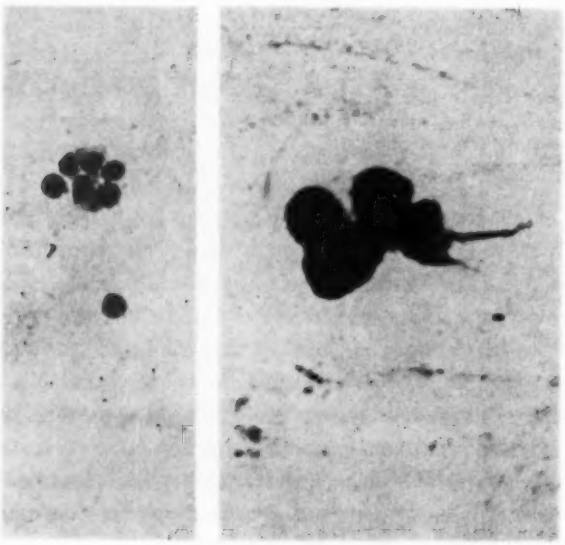
TABLE I

Total number of patients examined by smear	494
Number of cases without demonstrable malignancy	464
Number of cases correctly diagnosed as negative	454 (98%)
Number of cases incorrectly diagnosed as positive	8 (2%)
Number of cases with malignancy	32
Number of cases correctly diagnosed	26 (81%)
Number of cases incorrectly diagnosed as negative	6 (19%)

Of these, 462 had no known malignant disease. Four hundred and fifty-four, or 98 per cent, were correctly diagnosed as negative and eight, or 2 per cent, were incorrectly diagnosed as positive (false positive). The latter figure approximates the findings of Schmidlapp and Marshall.[8] The eight cases of false positive reports included: three cases of tuberculosis of the kidney; three of chronic pyelonephritis, two of which were complicated by calculi; and two cases of acute pyelonephritis. Thirty-two patients had malignancy of the urinary tract, and of these, twenty-six, or 81 per cent, were correctly diagnosed, and six, or 19 per cent, were incorrectly diagnosed as negative (false negative). The twenty-six which were correctly diagnosed by smear consisted of nine renal tumors and seventeen bladder tumors. The six cases reported as negative included four which were renal tumors and two which were tumors of the bladder, all of which were reported as malignant on pathologic study.

Thus it appears that diagnosis is more accurate in bladder tumors than in renal tumors, and this is readily understandable due to the fact that vesical tumors are constantly bathed in urine, while renal tumors must either have invaded the collecting system, or arisen from the epithelium of this system, before malignant cells exfoliate. Fremont-Smith, Graham and Meigs[9] confirm this in their findings of 71 per cent accuracy for bladder malignancy, and 50 per cent accuracy for renal tumors. No attempt was made to classify the grade of the malignancy by the cells seen in the smears.

Report of Cases: The following three case reports demonstrate not only the value of urinary sediment examination in being able to find malignancy before the usual urologic measures are brought to bear, but also aid significantly in arriving at a clinical diagnosis which otherwise may prove to be difficult.



Case 1. Figure A: Single malignant cell, magnification 15x. Note hyperchromatism of nucleus, deepened staining reaction, and bizarre arrangement of the nucleoli.

Figure B: Group of malignant cells showing the same characteristics as the single cell. There is almost complete replacement of the cytoplasm by the enlarged nuclei. The giant size of the cells is to be compared with the inflammatory cells in the background.

Case 1: W.L., a 63 year old Negro male, was admitted to Bellevue Hospital on June 2, 1950, in a confused and disoriented state. The chief complaint was abdominal enlargement for the past five days. His past history was unobtainable.

Physical examination was essentially negative except for a large distended bladder, and a moderately enlarged prostate which was benign to palpation. The temperature was 103°F.

A urethral catheter was easily inserted. A specimen of urine was sent to the cytology laboratory at this time and a diagnosis of carcinoma was made.

Laboratory findings of importance were: 3-5 red blood cells and 14-16 white blood cells per high-powered field in the urine; non-protein-nitrogen—150 mg. per cent; urea nitrogen—90 mg. per cent; and a 4 plus serology for lues.

Intravenous pyelography was attempted but was unsuccessful. The urethral catheter did not function properly, and on June 20, a suprapubic cystotomy was performed. Two papillary tumors were found on the floor of the bladder. These were excised and fulgurated. A preliminary cystoscopy was not done because of the poor condition of the patient. The pathologic report was benign papilloma of the bladder. On July 1, 1950, the wound dehisced and was closed secondarily with no further complication. Three weeks later, a transurethral resection of the prostate was done, and the pathologic

report was benign hyperplasia of the prostate. Convalescence was uneventful, the cystotomy wound was permitted to close, and the patient was discharged to the outpatient department for further care. He did not attend the clinic, and was lost to follow-up. He was readmitted on February 18, 1952, with the complaint of moderate hematuria which began two weeks previously. He had felt perfectly well until this time. The hematuria was episodic and painless, and associated only with increased frequency of urination. Physical examination revealed a suprapubic mass, on the left side of the midline, which measured 5x7 cm. Non-protein-nitrogen was 22 mg. per cent, and the serology still 4 plus. The urine was again reported positive for carcinoma on cytologic examination.

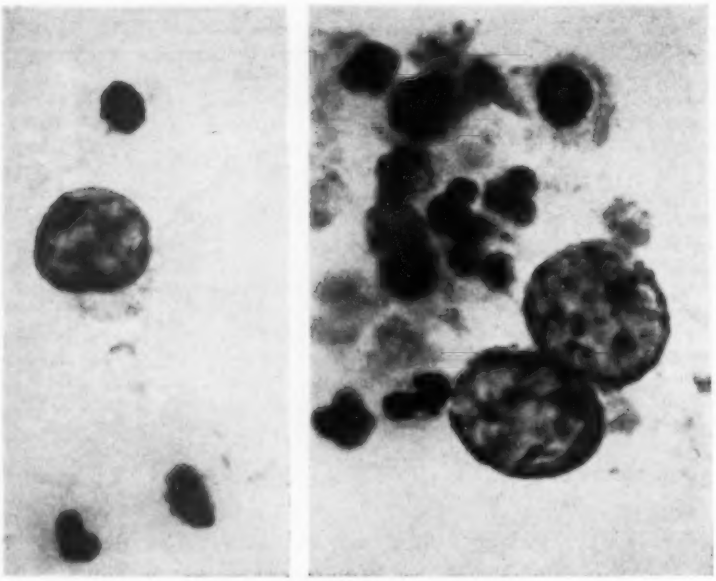
Cystoscopy was performed on February 20, 1952, and revealed a small recurrent tumor on the floor of the bladder, and several bleeding points in the vesical mucosa. The tumor was thoroughly fulgurated, and the bleeding points coagulated. Biopsy of the suprapubic mass was done, and reported as transitional-cell carcinoma of the bladder. Due to malignant extension beyond the bladder, irradiation was started, and the hematuria diminished to microscopic proportions. Again the patient was referred to the outpatient department, but again he failed to appear. He was last seen on September 10, 1952, when admission to the hospital was sought for the complaint of gross hematuria. Large amounts of tumor tissue were seen in the bladder, and the suprapubic mass was increased in size. The patient was deemed inoperable, and he was referred for balloon radiation therapy.

This case, it is believed, amply illustrates the value of examination of the urinary sediment in early diagnosis of malignancy of the urinary bladder. It is also thought that it bears out the value of the examination as a screening test. The cancer was discovered in a syndrome which appeared clinically as prostatic obstruction with acute urinary retention, the latter complication obscuring the underlying more significant pathology. It also demonstrates the error resulting when biopsy of only non-malignant portions of the growth is obtained.

Case 2: S.A., a white female, aged 74, single, was admitted to University Hospital on January 30, 1951, for the complaint of hematuria which was recurrent since July, 1949. She had undergone a thyroidectomy thirty years ago. Her history noted blood on her underclothes in July, 1949, which had occurred for one day only, and was not associated with pain. She thought it was vaginal in origin, and payed no attention to it until a similar episode took place one month later. She was admitted to a hospital where a dilatation and curettage were performed, but no definite pathology of the endometrium was discovered. Bleeding again occurred in November 1950, but this time was definitely noted in the urine, and was not associated with any symptoms. The sole urologic complaint was nocturia 1-2 times, for years.

Physical examination revealed only a soft systolic apical murmur due to arteriosclerosis. The urine was sent to the laboratory for smear examination and was reported as positive for malignancy. Urine analysis was essentially negative as were blood chemistry and serology.

Cystoscopy and retrograde pyelography were performed on February 1, 1951, and the bladder was found to be normal. Specimens from both renal pelves were sent for cytologic examination, and the smear from the left side was positive. Pyelograms showed an irregular filling defect in the renal pelvis, on the left. The calyx emptying the superior pole was distended, while the remaining calyces were normal. A delayed film revealed one hour stasis of the dye in the superior calyx. The pyelogram on the right



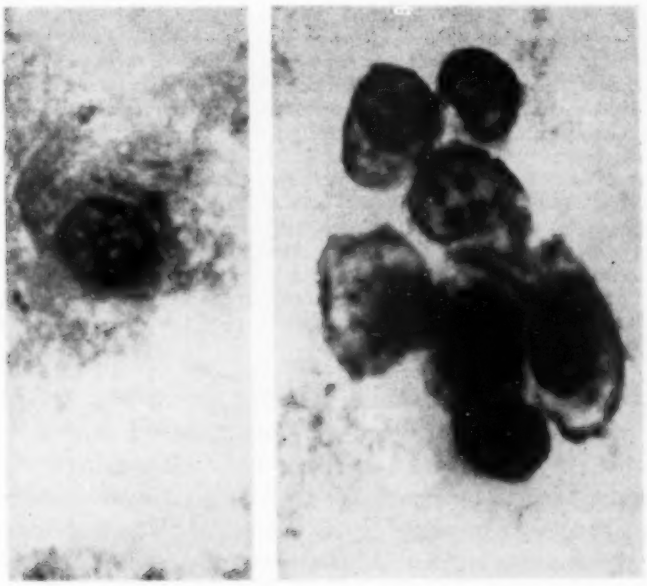
Case 2. Figure A: Low power magnification of a cluster of cells showing intense staining reaction, and irregularity in the size and shape of the nuclei.

Figure B: High power magnification of another cluster revealing marked hyperchromatism, loss of cell outline, anisocytosis, and altogether bizarre appearance.

side was essentially normal. The x-ray diagnosis was- "possible tumor of the left renal pelvis."

The patient refused operation at this time, and was readmitted for surgery on April 18, 1951. In the interim, she had been hospitalized for pneumonia. An admission urine was sent for cytologic examination and again was reported positive for malignancy. Repeat pyelograms were unchanged. X-ray of the chest was negative for metastasis. On May 4, 1951, after preoperative preparation, a left nephrectomy was performed through a lumbar incision. The pathology report was epidermoid carcinoma of the left renal pelvis and uretero-pelvic junction. Convalesence was uneventful, and she was discharged for care at home, on May 16, 1951.

The above case, although retrograde studies revealed the possibility of malignancy of the renal pelvis, did confirm the clinical suspicion and left no doubt in the surgeon's mind concerning the problem with which he was confronted. It may be assumed that had examination of the urinary sediment been done at an earlier date, the neoplasm would have been detected, and the surgery performed sooner.



Case 3. Figure A: 15x magnification of a single cell showing an increase in nucleoli formation, marginal condensation of chromatin, and enlargement of the nucleus.

Figure B: A cluster of cells showing irregularity in size, shape, and appearance of the cells. There is irregularity of staining of the nuclei, and in nucleoli formation. Some cell outlines are lost. There is a general appearance of disorder.

Case 5: C.G., a 41 year old white male, admitted to Lenox Hill Hospital on March 4, 1952, with the chief complaint of "feeling something in his stomach which if it was removed would make him feel better." His history stated that in October 1951, he felt a gradual onset of dull distress in his epigastrium which occurred one-half-one hour after meals, and occasionally awakened him from sleep. He was told that he had an ulcer. He was placed on a diet, with some relief. In December, 1951, he had gall-bladder and gastrointestinal studies, with no pathology being found. The pain had become progressively worse, and was now associated with anorexia. His past history included the removal of his left testicle in 1939, for adenocarcinoma, followed by x-ray therapy of unknown amount or duration.

Physical examination revealed a hard, nodular mass filling the epigastrium and right upper abdomen, and extending to the level of the umbilicus. It moved slightly with respiration. There were round, firm, movable, enlarged right axillary lymph nodes. The left testicle was absent.

Examination of the urinary sediment was positive for malignancy.

Laboratory findings of significance were: negative liver function tests; negative Ascheim-Zondek test; 1-2 red blood cells and 4-8 white blood cells per high-powered field in the urine with cultures of enterococcus and Staphylococcus albus.

Cystoscopy and retrograde pyelography were performed on March 5, 1952, and the bladder and left pyelogram appeared normal. The right pyelogram showed incomplete filling of the superior calyx, and displacement of the right kidney downward and laterally. Chest x-ray revealed a density at the base of the right lung, and upward displacement of the right diaphragm.

Biopsy of a node from the right axilla was done on March 11, 1952, and the diagnosis was reticulum cell lymphosarcoma. The patient was given x-ray therapy over the right renal area with 15x15 cm. portal, receiving a total of 4000 r. He improved symptomatically, and was discharged on March 30, 1952. He returned in April, with exacerbation of his previous complaints. His condition deteriorated progressively and he expired on May 5, 1952.

Autopsy was performed and a retroperitoneal lymphosarcoma with invasion of the *left* kidney capsule and renal parenchyma in the upper pole was found. In addition acute pyelonephritis was present.

Although a primary malignancy of the kidney was not present in this case, and pyelography suggested that there was a right renal involvement, this test did reveal that a neoplasm was invading a portion of the urinary tract. The autopsy showed the invasion to be in the left kidney. This was not suspected on pyelography. The test diagnosed a tumor which was corroborated by biopsy.

The eight cases which were diagnosed as false positive confirm the findings of other investigators, that the presence of calculi, chronic irritation, or inflammation, often produce metaplastic changes in the urothelium. These closely resemble the criteria upon which a positive diagnosis of malignancy is made. These errors can only be eliminated or reduced by the increasing familiarity of the examiner with cells of this type. However, in such instances, no surgical intervention is undertaken until the diagnosis is supported by evidence derived from pyelography, or other procedures available to the urologist. If no clinical manifestations of malignancy are found, repeated studies are performed. These include both clinical and exfoliative cytologic examinations, over an extended period of time, until all possibility of malignancy is ruled out.

It is felt that the false negative diagnoses are not too significant, although of course, they are not desirable in any screening process. The symptomatology plus the diagnostic facilities of the urologist almost invariably lead to the correct diagnosis, or at least, to the indications for surgical investigation.

Summary

1. The urines of 494 patients who had all types of urologic disease, excepting those with a urethral discharge, were examined by staining the sediment and examining the exfoliated cells.

2. Only the names and ages of the patients were known to the examiner.

3. Four hundred and sixty-two patients had no malignancy, and 98 per cent of these were correctly diagnosed. Eight, or 2 per cent, were incorrectly diagnosed.

4. Thirty-two patients had malignancy of the urinary tract, and of these, twenty-six or 81 per cent, were correctly diagnosed, and six, or 19 per cent, were incorrectly diagnosed.

5. Three cases were abstracted to illustrate the value of the examination, not only in detecting malignancy, but also in aiding the urologist in arriving at a correct clinical diagnosis.

Conclusion: It is believed that the exfoliative cytologic examination of the urine is valuable as a screening test for malignancy of the urinary tract, but it is not intended to replace the usual urologic procedures.

Grateful acknowledgment is made to Drs. Robert S. Hotchkiss and George W. Slaughter for permission to use cases from their private services.

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EXPERIMENTAL EPILEPSY IN THE MONKEY FOLLOWING MULTIPLE INTRACEREBRAL INJECTIONS OF ALUMINA CREAM*

JOSEPH G. CHUSID,† LENORE M. KOPELOFF, Ph.D. and NICHOLAS KOPELOFF, Ph.D.

THE multiple intracerebral injection of alumina cream (aluminum hydroxide cream) into a principal cerebral sensorimotor cortical area is effective in producing chronic epilepsy in monkeys.[1] Some of the clinical, pathological and electroencephalographic features of such epileptic animals, supplemented by a motion picture demonstration of a reactive monkey, are the subject of the present report.

Method: Alumina cream was injected into eight areas of the exposed sensorimotor cortex of one cerebral hemisphere (Fig. 1) in six Macaca mulatta and into both cerebral hemispheres in an additional monkey. Injections of 0.1 ml. alumina cream were made slowly through a 26 gauge hypodermic needle inserted almost perpendicularly to a depth of 3 to 11 mm. The estimated amount of alumina cream retained in each cerebral hemisphere following injection varied from 0.3 to 0.6 ml. Animals were observed following operation for periods up to nine and one-half months, during which time serial electroencephalograms (EEG), clinical observations and motion picture studies were made. Brains were studied postmortem and the injection sites plotted.

Results: In all injected animals a variable degree of contralateral hemiparesis was obvious immediately after operation. In five of the six monkeys injected unilaterally, spontaneous contralateral focal motor seizures were evident three to four weeks after operation. Initially there occurred almost continuous twitch-like movements of varying amplitude and regularity, involving the musculature of the contralateral face and limbs. Excitement, agitation, movement or stress readily aggravated and accentuated this type of motor activity and sometimes led

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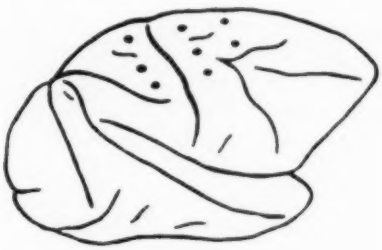

Figure 1. Diagram of lateral aspect of cerebral hemisphere of Macaca mulatta with sites of injection indicated by heavy dots.

to Jacksonian spread with full-blown generalized convulsive seizure and exhaustion. During the following few weeks, spontaneously occurring Jacksonian motor seizures with spread became a more prominent feature. The twitch-like muscle movements then became less evident, the animals continuing to exhibit spontaneous Jacksonian seizures and marked susceptibility to motor seizures by prodding or stress. These animals thereafter resembled in their epileptic behavior other monkeys made epileptic by application of a disc containing alumina cream to one sensorimotor cortex.[2] The monkey in which multiple injections were made into both cerebral hemispheres expired in generalized status epilepticus two weeks after the onset of seizures and five weeks after operation despite treatment with large doses of parenteral phenobarbital.

Postmortem examination of the brains disclosed a meningocerebral cicatrix extending over the zone of cerebral injections with scarring of the underlying cortex and subcortical white matter. The sites and needle tracks of alumina cream injections were in general grossly visible in coronal sections. Microscopic examination revealed that the needle tracks contained masses of more or less homogenous injection mass with collections of gitter cells most prominent near the borders. The reaction of the brain tissue around the deposits of alumina cream was variable and in some areas a minimal pathological reaction was seen. Vascular zones containing many vessels with thickened endothelial layers projected from some edges of the needle tracks (Fig. 2). Cerebral tissue adjacent to the tracks frequently showed evidence of severe neuronal changes, intense astrocytic gliosis, markedly increased vascularity and demyelinization of subcortical white matter. The deep-

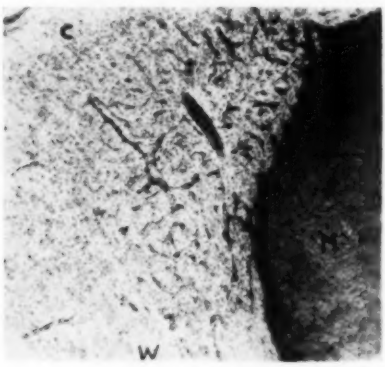

Figure 2. Cerebral area bordering injection mass (M) with reactive vascular zone extending into cortex (C) and adjacent white matter (W). (H & E x 68). Monkey #653.

est injections (11 mm.) were made in the only monkey which did not exhibit spontaneous seizures, and extended into the superior putamen and internal capsule. Occasional small cyst formation was evident at some injection sites.

Following multiple intracerebral injections of alumina cream pronounced changes occurred in the electroencephalogram (Fig. 3). During the initial, relatively continuous convulsive phase, high amplitude (300-400 μv) serial spike, or spike and slow wave formations were most pronounced over the injected cerebral site. In the following stage this type of abnormality gradually became less evident, the tracings showing an increased amount of mildly slowed frequencies of increased amplitude. The rapid intravenous injection of 0.1 to 0.15 ml. 10 per cent Metrazol at this time usually promptly provoked focal random or serial high amplitude spike discharges, and was sometimes accompanied by motor convulsive manifestations. In electrocorticograms made from exposed brain and scarred area (Nembutal anesthesia) runs of serial spikes and random spike activity were present simultaneously in widely separated areas. In the monkey with the shallowest injections (3 mm.) the EEG was unusual in that recurrent spindle bursts of fast activity (18-22/sec.) occurred over the injected site (Fig. 4). Apparent transmission of spike, or spike and slow wave activity to homologous areas of the non-

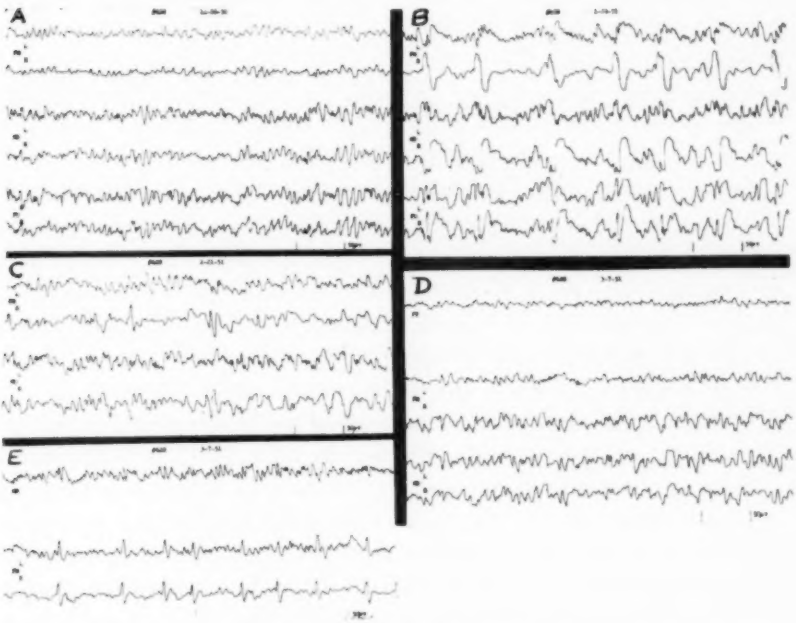

Figure 3. Serial electroencephalograms of monkey #628 following multiple intracerebral injections of alumina cream.

A 12/26/50 Control preoperative tracing.
B 1/25/51 4 weeks after injection.
C 2/21/51 8 weeks after injection.
D 3/7/51 10 weeks after injection.
E 3/7/51 10 weeks after injection following intravenous Metrazol (10 mg.).

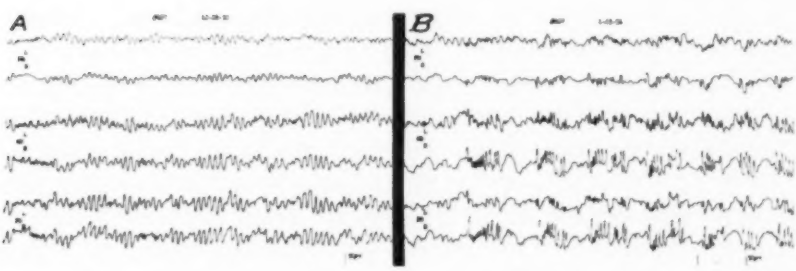

Figure 4. Electroencephalograms in monkey #627 with shallow injections.

A 12/26/50 Control preoperative tracing.
B 1/25/51 4 weeks after injection.

injected cerebral hemisphere commonly occurred, with these patterns most evident in the first weeks following onset of motor convulsive activity.

Discussion

The focal motor epileptic manifestations present at the onset of epilepsy in the monkeys following multiple intracerebral sensorimotor injections of aluminum hydroxide cream so closely resembled human epilepsia partialis continua that they would appear to be the simian counterpart. The form of human motor epilepsy known as epilepsia partialis continua was first reported by Koshewnikow.*[3] Wilson[4] described epilepsia partialis continua as "Another motor variant, doubtless somewhat rare, differs from the general myoclonic type in that the twitching is limited to one segment of the body (hence the term 'mono-epilepsy') nearly always peripheral, such as wrist and fingers, is virtually continuous between infrequent paroxysmal Jacksonian generalized fits, and on the whole consists less in formed movements than in irregular muscular contractions. Known also as 'polyclonia epileptoides continua', most though not all of the reported cases have had a background of structural disease of the cortex." Penfield and Erickson[5] stated that epilepsia partialis continua "may be defined as a local convulsive movement of one part of the body which continues steadily, or with brief interruptions, over long periods of time. It may be a localized continuing myoclonic seizure, or it may be a simple focal motor seizure in which discharge does not spread across the cerebral cortex but remains limited." Radermecker and van Bogaert[6] among others, have emphasized that "Kojewnikoff epilepsy" clinically resembles excitation or liberation of the cortex and noted that there exists a whole range of transitions between the unilateral clonic movements in some cases of "ordinary" epilepsy and epilepsia partialis continua.

Since the injections of alumina cream were made intra- and subcortically the essential clinical and pathophysiological changes are believed to have resulted from local cortical and superficial subcortical white matter changes. Motor function for the principal cerebral sensory as well as for the motor area has been well established in the monkey[7, 8] so that in these injected animals a wide area of cortical and subcortical chronic motor facilitation and stimulation was probably

* Also referred to as Kojewnikoff, Koschewnikoff, Koschewnikow or Kojewnikov.

achieved. A similar clinical reaction occurred in a previously unreported monkey with multiple intracerebral injections of alumina cream confined to a precentral motor zone (Area FA, FB, FBA); a like result was obtained with multiple injections of alumina cream confined to a post-central gyrus (Area PE, PEm). It should be noted in this connection that Töbel and Schaltenbrand[9] reported a human case of "Kojewnikoff syndrome" associated with a small abscess located in the white matter of a parietal lobe near the junction of cortex and subcortical white matter.

We do not know why motor epilepsia partialis continua rather than ordinary Jacksonian convulsions or seizures with Jacksonian spread occurred in the early stages of the epileptic reaction. One may speculate that spread of impulses from any single site to produce a Jacksonian seizure may have been hindered by a local relative refractory state following the more or less constant asynchronous excitation of the various cortical zones injected. Intracortical spread of excitation may have been more difficult at this stage because the stimulant effect was produced in deeper cortical zones and in subcortex distal to the superficial layers of cerebral cortex. The possibility also exists that the threshold for motor excitation of deeper, efferent cortical cells and fibers of the sensorimotor cortex was considerably less than that of other routes of transmission. Irregular stimulation of small aggregates of motor efferent cells of insufficient magnitude to reach a critical value or form necessary for Jacksonian spread might also have been a factor. Furthermore, the injection treatment may have shortcircuited intracortical relays so that involvement and participation of full-thickness cortical neuronal chains occurred rarely or only under the facilitating effect of agitation, stress, movement or excitement.

During the early epileptic phase, the electroencephalograms contained more or less continuous high amplitude spike, or spike and slow wave discharges, most intense over the cerebral site that had been injected. These patterns persisted during phases of intense epilepsia partialis continua, becoming less prominent thereafter. When relatively small muscle segments were involved in twitching or myoclonic responses, a direct correlation between components of the electroencephalogram and visible abnormal muscle motor activity could not be established. Occasionally, for short periods of time, especially when more massive focal myoclonic responses occurred, spike discharges in the EEG seemed

to occur synchronously with visible abnormal motor activity. During the ensuing stages, spike activity was generally replaced by high amplitude serial slow wave activity. Intravenous Metrazol (0.1 to 0.15 ml. 10 per cent solution) promptly evoked spike, or spike and wave discharges from the injection sites and frequently also from the homologous contralateral cerebral area. Although such responses might occur without visible motor reaction, at times they were associated with or soon followed by a focal myoclonic, Jacksonian or generalized motor seizure. Spindle bursts of fast activity such as occurred in the monkey with shallow intracerebral injections represent a highly unusual EEG pattern in epileptic monkeys and are ordinarily not associated with the epilepsy which follows application of alumina by disc to the cerebrocortical sensorimotor surface.

Summary

1. Clinical, pathological and electroencephalographic features of monkeys made epileptic by multiple intracerebral injections of alumina cream into a principal sensorimotor area are presented.

2. The early motor convulsive manifestations in such epileptic monkeys resemble the motor form of human epilepsy described as epilepsia partialis continua (Koshewnikow).

We wish to thank F. A. Simpson, D. Livingston and F. Romagnoli for their technical assistance.

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ROBERT B. HIATT—Instructor in Surgery, College of Physicians and Surgeons, Columbia University

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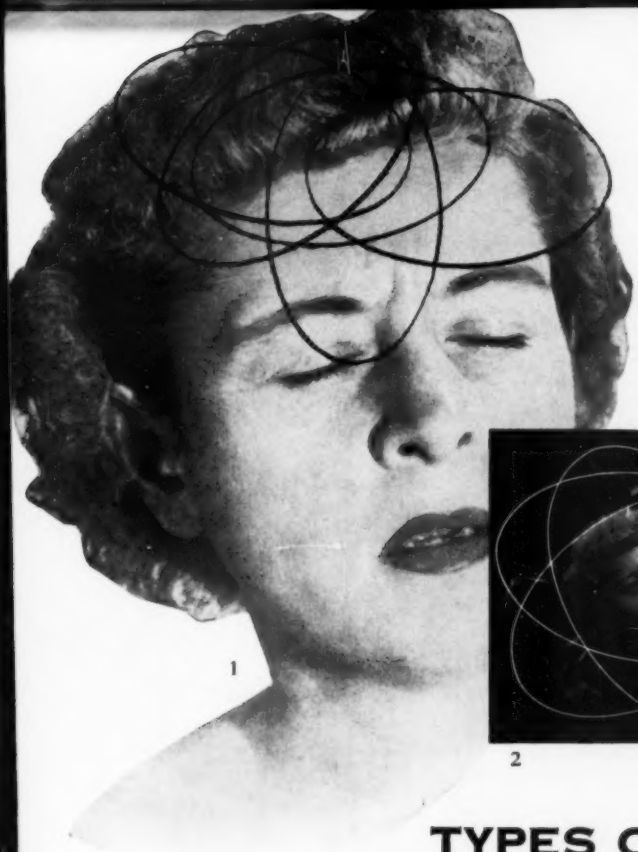

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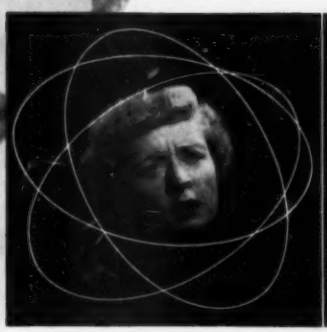
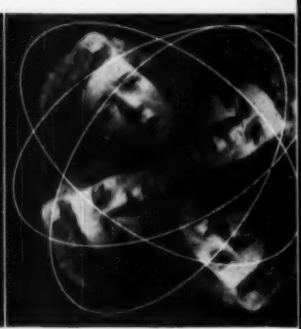
2. *Objective vertigo . . . the environment is in motion.*
3. *Subjective vertigo . . . the patient himself moves in space.*





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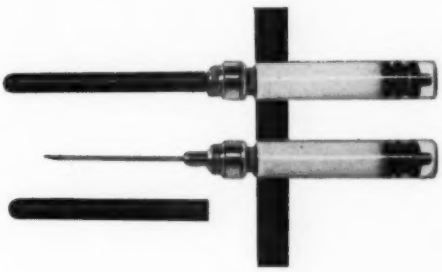

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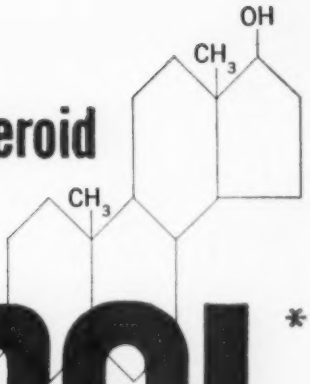

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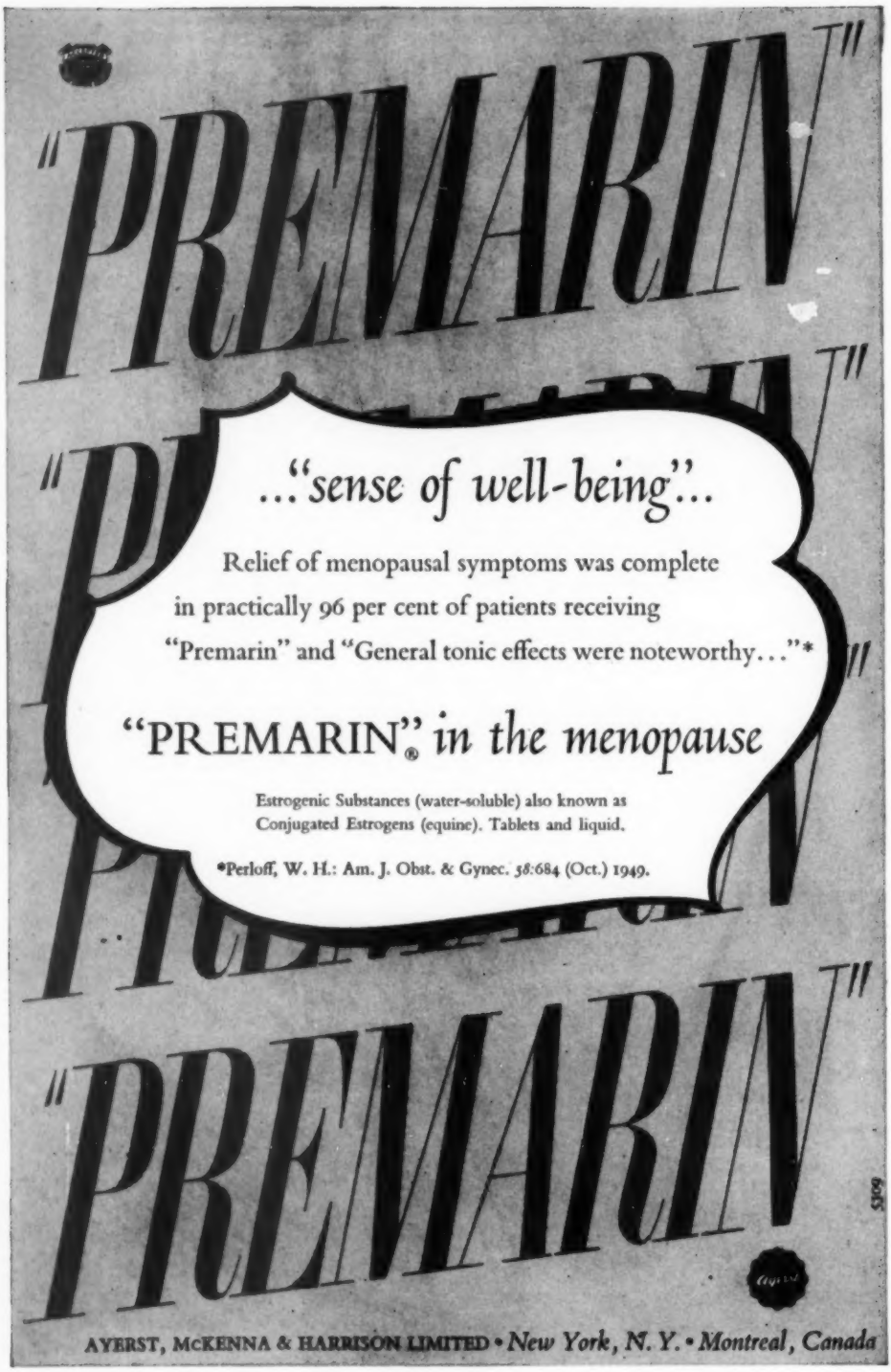
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*Perloff, W. H.: Am. J. Obst. & Gynec. 58:684 (Oct.) 1949.
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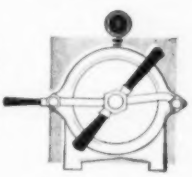

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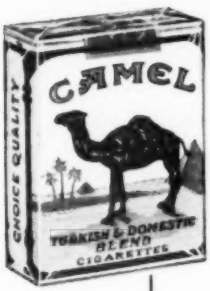

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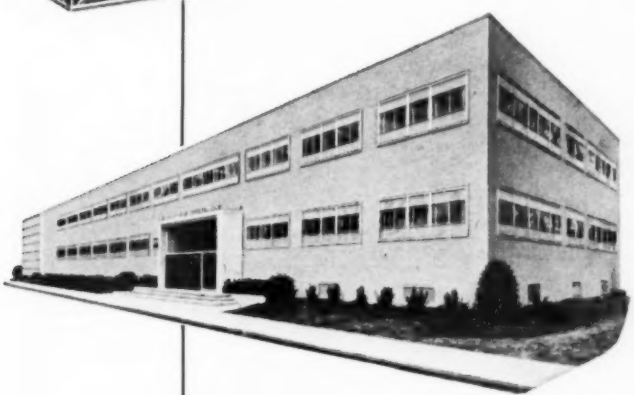

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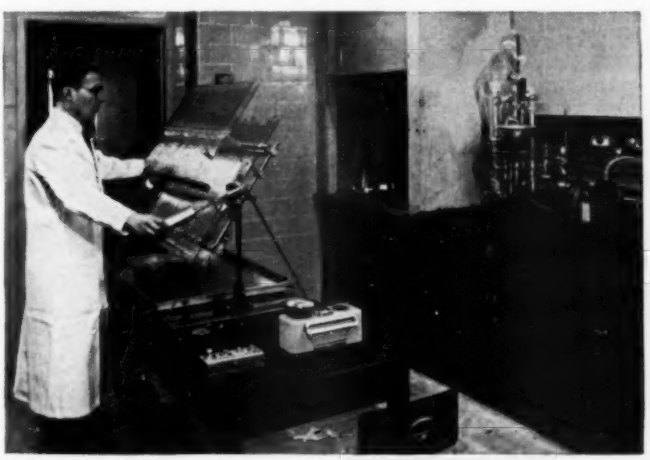

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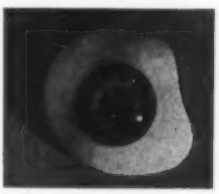

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